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# The Chemistry on Diterpenoids in 1971

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CITATION:

Fujita, Eiichi. The Chemistry on Diterpenoids in 1971. Bulletin of the Institute for Chemical Research, Kyoto University 1974, 52(3): 519-560

ISSUE DATE:

1974-12-25

URL:

<http://hdl.handle.net/2433/76566>

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## Review

# The Chemistry on Diterpenoids in 1971

Eiichi FUJITA\*

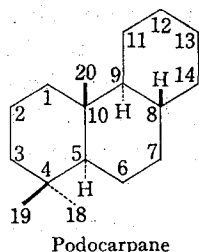
Received May 7, 1974

## I. INTRODUCTION

This is one of a series of annual reviews<sup>1-7)</sup> on diterpenoids chemistry by the author.

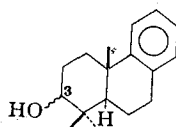
In principle, in each section the full papers were first described and the short communications followed. The order of the journals followed the alphabet of their names.

## II. PODOCARPANE DERIVATIVES\*\*

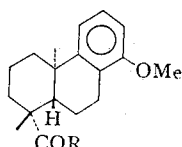


Oxidative cyclization of 4,8-dimethyl-1-phenyl-3,7-nonadiene with benzoyl peroxide was tried. From the *trans*-3-ene, podocarpene derivatives **1** (18%) and **2** (2~3%) were formed, while the *cis*-isomer gave only very low yield (3%) of **1**.<sup>8)</sup>

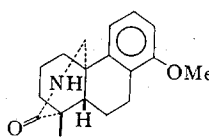
Racemic acid **3** was converted into azide **4**, which, without purification, was irradiated with a high-pressure



**1**: 3β-OH  
**2**: 3α-OH



**3**: R=OH  
**4**: R=N<sub>3</sub>



**5**

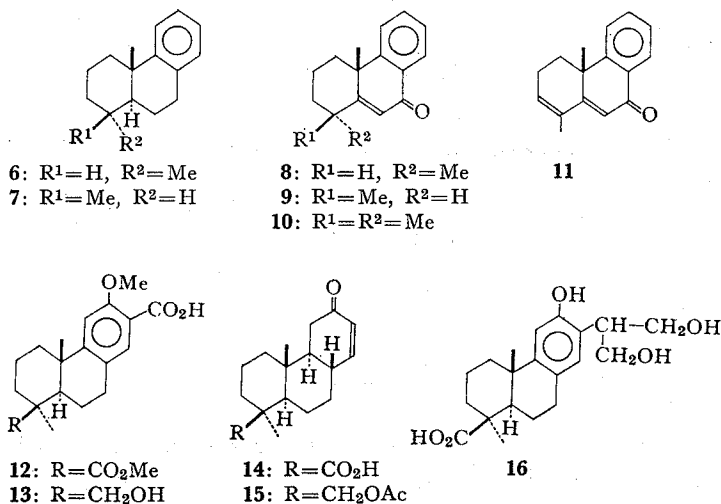
mercury lamp to give a δ-lactam **5**.<sup>9)</sup> Since this lactam had been converted into the *Garrya* alkaloids, this completed another formal total synthesis of garryine, veatchine, and atisine.

Deisopropyldehydroabietane derivatives and related substances, **6-11**, were synthesized and their UV spectra and ORD curves were analyzed.<sup>10)</sup>

Lithium in liquid ammonia reduction of ester **12** and hydroxy acid **13** with concomitant decarboxylation provided a good route to moderate yields of the α,β-unsaturated ketones, **14** and **15**. The ketone **15** was also prepared in improved yield by another method.<sup>11)</sup>

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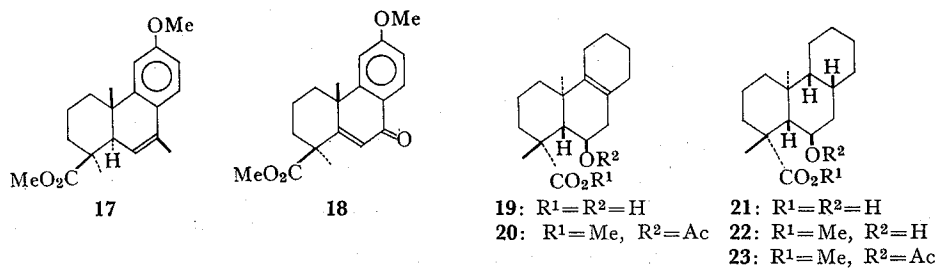
\*\* See also ref. 108 (Section IX).



The reactions of boron trifluoride and dimethyl sulfoxide on ring-A epoxy derivatives of 18-norabieta-8,11,13-triene and 12-methoxy-18-norpodocarpa-8,11,13-triene were carried out, and the mode of formation of the products were discussed.<sup>12)</sup> The stereochemistry of 6-bromo-7-oxo derivatives of diterpenoids possessing an aromatic ring C was discussed. The assignment of configuration of 6-bromo substituents from NMR and NOE data was examined and limitations to the use of the ORD curves were discussed.<sup>13)</sup>

The structure of pododacric acid, a trihydroxy diterpenoid acid obtained from New Zealand *Podocarpus* species, was determined as **16** and confirmed by partial synthesis from podocarpic acid.<sup>14)</sup>

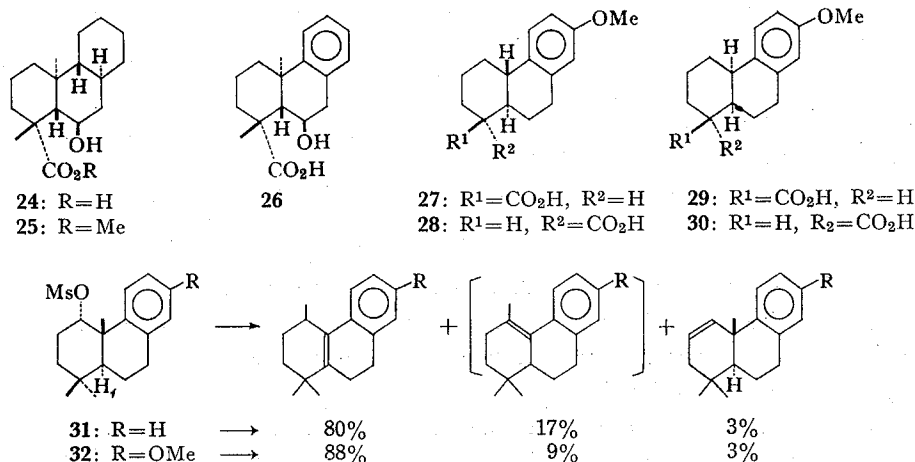
The dichromate oxidation of **17** to **18** was reported, and the mechanism pathway of the oxidation was provided.<sup>15)</sup>



Reduction of *ent*-6 $\alpha$ -hydroxypodocarpa-8,11,13-trien-19-oic acid derivatives provided a route of synthesizing compounds **19** to **25**.<sup>16)</sup> Epimerization of 6 $\beta$ -hydroxy group at lactonization was recognized on compounds **19** and **21** as experienced about **26**, but not on **24**.<sup>17)</sup>

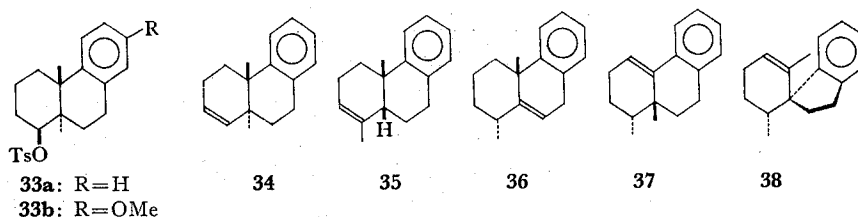
All four possible racemates of 1-carboxy-1-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrenes, **27–30**, were synthesized.<sup>18)</sup>

Compounds **31** and **32** were synthesized and their solvolytic rearrangement was investigated. Products arising from acetolysis of **31** and **32** and their yields are shown in Scheme 1.<sup>19)</sup>

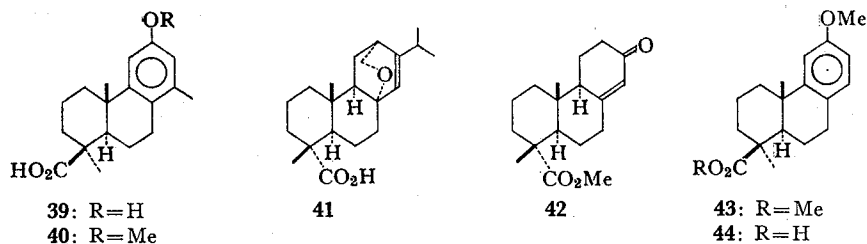


Scheme 1

Buffered solvolysis of **33a** afforded the unrearranged olefin **34**, the singly backbone rearranged olefins, **35** and **36**, the doubly backbone rearranged olefin **37**, and aryl migrated olefin **38**. Similar products were obtained from solvolysis of **33b**.<sup>20)</sup>



Racemic 14-methylpodocarpic acid (**39**) and O-methyl-14-methylpodocarpic acid (**40**) were synthesized.<sup>21)</sup>

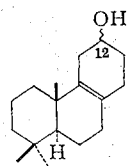


Phenols of the podocarpic acid series were oxidized in ring B at room temperature with 2,3-dichloro-5,6-dicyanobenzoquinone in alcoholic solvents. Two equivalents of the quinone yielded mainly the corresponding 7-ketones, while the use of three equivalents provided a convenient one-step synthesis of the 5,6-dehydro-7-ketones.<sup>22)</sup>

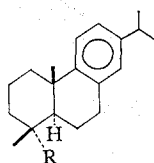
Levopimaric acid-formaldehyde adduct **41** was converted into methyl podocarp-8(14)-en-13-on-18-oate (**42**) *via* five steps.<sup>23)</sup>

Cleavage of sterically hindered esters, *e.g.* methyl O-methylpodocarpate (**43**), was achieved by the use of boron trichloride to yield 90% of O-methyl podocarpic acid (**44**).<sup>24)</sup>

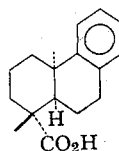
The conformation of ring C in alcohols **45** and **46** was investigated by NMR, and they



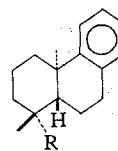
45: 12 $\beta$ -OH  
46: 12 $\alpha$ -OH



47: R=CO<sub>2</sub>N  
48: R=CN



49

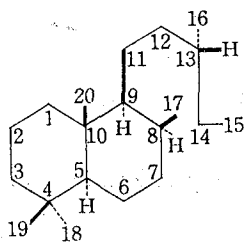


50: R=CO<sub>2</sub>Me  
51: R=CN

were shown to have the preferred half-chair conformation in ring C. This conformation was exactly analogous to that preferred in ring A of the 5(10)-estrene series. The close correspondence of molecular rotation differences between these two series provided further support for these conclusions.<sup>25)</sup>

Transformations of the diterpene A/B ring juncture to the antipodal system were carried out starting from **47** and **48**. Acid **47** was converted into A/B *cis* product **49** by reverse Friedel-Crafts reaction, and methyl ester of **49** was subjected to isomerization into **50** by treatment with 10% palladium-carbon in refluxing triglyme for 3 hours. Ester **50** was converted into methyl *ent*-podocarpate. Similarly, nitril **48** was transformed into **51**.<sup>26)</sup>

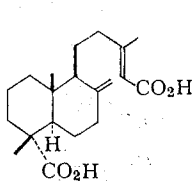
### III. LABDANE DERIVATIVES\*



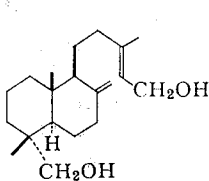
Labdane

A diterpene acid, dehydropinifolic acid, was isolated from the needles of *Pinus silvestris* and shown to have structure **52**.<sup>27)</sup> The labdane diterpenes, 4-epiagathadiol (rayadiol) (**53**), 18-hydroxymanool (torreferol) (**54**), and 18-hydroxy-13-epimanool (13-epitorreferol) (**55**) were isolated from the non-steam volatile fraction of the leaves of *Torreya nucifera*.<sup>28)</sup>

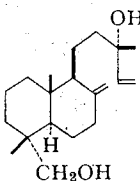
Copalic acid (**56**), *ent*-3-hydroxyabda-8(20),13-dien-



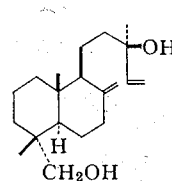
52



53



54

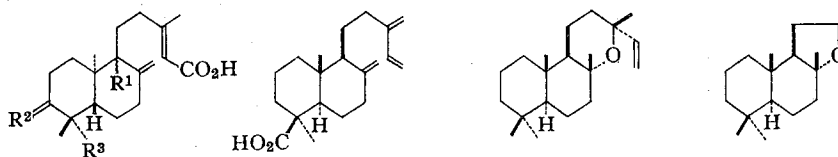


55

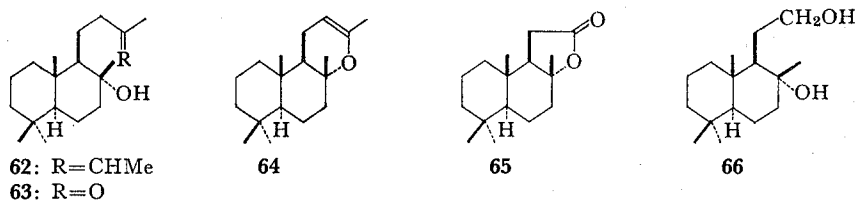
15-oic acid (**57**), and *ent*-agathic acid (**58**) were isolated from *Copaiba* oil. Their structures were determined by their spectroscopic data and those of their derivatives and by comparison with their known derivatives.<sup>29)</sup>

A new diterpenoid acid, labda-8(17), 13(16), 14-trien-19-oic acid (**59**) was isolated from the oleoresin of *Callitris columellaris*. The known diterpenoids were also isolated.<sup>30)</sup> The structures of fourteen products derived from the selenium dehydrogenation of manool (**72**) were determined.<sup>31)</sup>

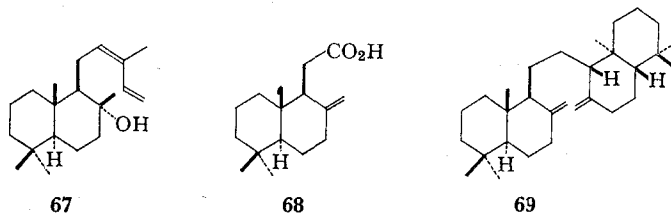
\* See also section V (ref. 63).

56:  $R^1 = \beta\text{-H}$ ,  $R^2 = \text{H}_2$ ,  $R^3 = \text{Me}$     5957:  $R^1 = \beta\text{-H}$ ,  $R^2 = \text{H}$ ,  $\text{OH}$ ,  $R^3 = \text{Me}$ 58:  $R^1 = \beta\text{-H}$ ,  $R^2 = \text{H}_2$ ,  $R^3 = \text{CO}_2\text{H}$ 

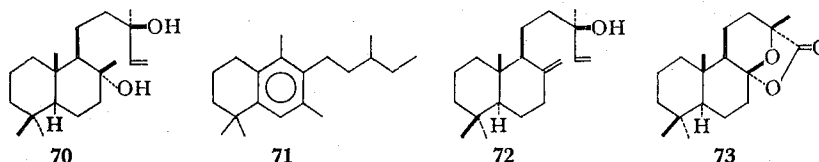
Manoyl oxide (60) was converted into the known five-membered oxide 61 with an ambergris-type odor, *via* intermediates 62–66. The oxide 61 was also prepared from manoyl oxide in two steps by oxidation with chromic anhydride followed by reduction of the lactone 65 with diborane.<sup>32)</sup>

62:  $R = \text{CHMe}$ 63:  $R = \text{O}$ 

A synthesis of  $\alpha$ -onoceradiene (69) from abienol (67) was reported *via* the Kolbe electrolysis of the key intermediate 68. The observed molecular rotation did not fit the predicted value.<sup>33)</sup>

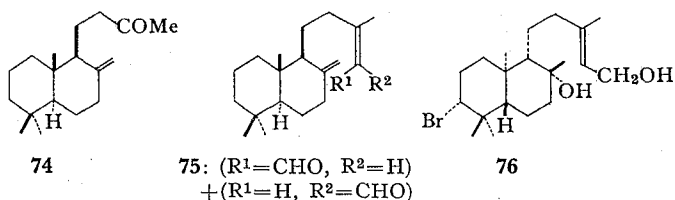


Structure 71 was assigned<sup>34)</sup> to the hydrocarbon first prepared by Ruzicka<sup>35)</sup> through the high temperature acid-catalyzed dehydration of sclareol (70).



Some products from the oxidation of manool (72) were examined. Potassium permanganate gave, *inter alia*, the hitherto unreported compound 73, while sodium dichromate gave the methyl ketone 74, and, as the major product, a mixture of (Z)- and (E)- $\alpha,\beta$ -unsaturated aldehyde 75. Some oxidations of 74 were examined.<sup>36)</sup>

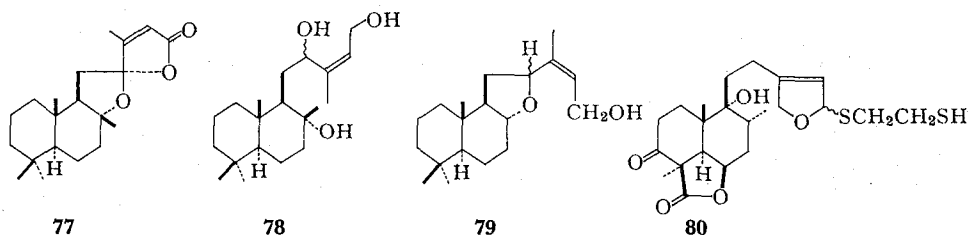
The selenium dehydrogenation of agathic acid (antipode of 58) was carried out, and a consistent scheme from dehydrogenation of intermediates was proposed. The dehydro-



genation of methyl sandaracopimarate was also examined.<sup>37)</sup>

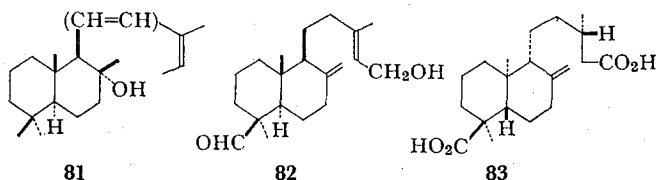
Two bromo-compounds, aplysin and aplysinol, had been isolated and characterized. The third minor bromo-compound, aplysin 20, had also been isolated from *Aplysia kurodai*.<sup>38)</sup> The structure of aplysin 20 was determined by X-ray analysis as **76**.<sup>39)</sup>

Triol **78** derived from  $\alpha$ -levantenolide (**77**) by treatment with lithium aluminum hydride was cyclized to compound **79** by treatment with stannic chloride.<sup>40)</sup>



3-Ketomarrubiin was treated with ethane-1,2-dithiol in the presence of boron trifluoride etherate to yield a 2,5-dihydro-2-(2-mercaptoethylthio)-furan derivative (**80**).<sup>41)</sup>

Diterpenoids from the oleoresin of *Pinus koraiensis* were separated by column chromatography. As the labdane derivatives, neoabienol (**81**) and isoagatholal (**82**) were isolated. The trisubstituted double bond in neoabienol was shown to have the Z-configuration.<sup>42)</sup>

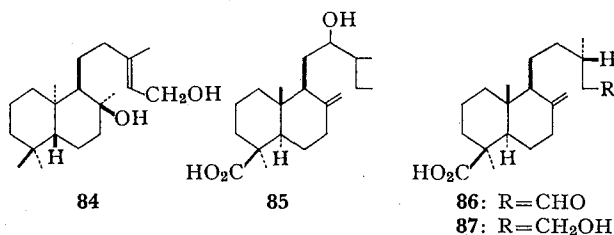


From the oleoresin of *Copaiifera langsdorfii*, ent-8(17)-labdene-15,18-dioic acid (**83**) was isolated.<sup>43)</sup> Anticopalic acid (antipode of **56**) was found to be a major resin acid in the bark and in the wood of *Pinus monticola*.<sup>44)</sup> From a light petroleum extract of *Juniperus phoenicea*, manoyl oxide, diol **84**, and a new hydroxy acid **85** were isolated.<sup>45)\*</sup>

From *Cistus labdaniferus*, labdane-8 $\alpha$ ,15,19-triol was isolated.<sup>46)\*\*</sup> A new diterpene, imbricatolalic acid (**86**) was found to be present as a major constituent in *Pinus elliottii* needles and *Cortex* oleoresin. The closely related imbricatolalic acid (**87**), previously reported only in *Araucaria imbricata*, was found in small amounts in slash pine needle extract.<sup>47)</sup>

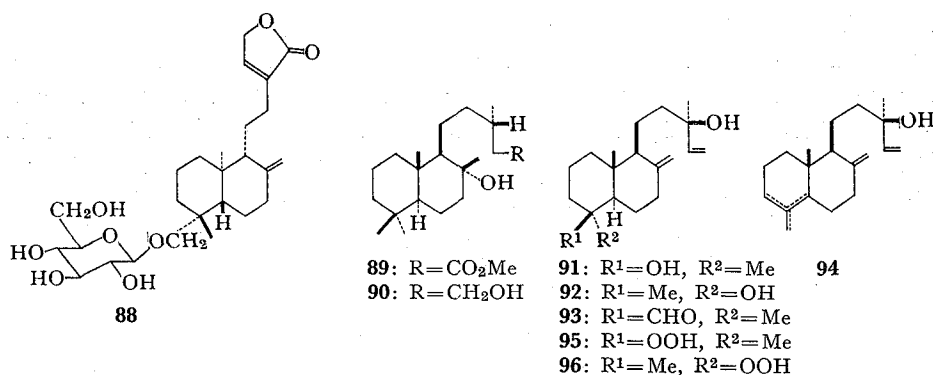
\* See also section V.

\*\* See also section IV.



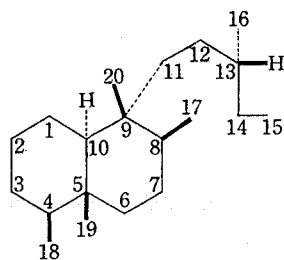
The investigation on the second, minor crystalline component, neoandrographolide isolated from the shrub of *Andrographis paniculata* led to the structure and stereochemistry shown in **88**.<sup>48)</sup>

The reduction of methyl labdanolate (**89**) with lithium aluminum hydride gave labdane-8,15-diol (**90**) which with tosyl chloride in pyridine gave the monotosylate. Treatment of the monotosylate with lithium aluminum hydride gave tetrahydroabienol. Thus, the 13-R configuration of tetrahydroabienol was determined.<sup>49)</sup>



The isolation in small amount from *Araucaria excelsa* of two new nor-diterpene diols **91** and **92** had been reported, but a pure sample of torulosal (**93**), which was among the components of the oleoresin from *A. excelsa*, kept five hours at room temperature without any solvent, when adsorbed on alumina or silica gel and then eluted with benzene yielded only 40% of starting aldehyde beside a less polar fraction containing a mixture of noralkenes **94** (9%) and a more polar fraction containing four substances. Two of them were **91** (0.6%) and **92** (5.5%). The other two were proved to be **95** (10%) and **96** (14%). Thus, these nor diterpenes may be artefacts.<sup>50)</sup>

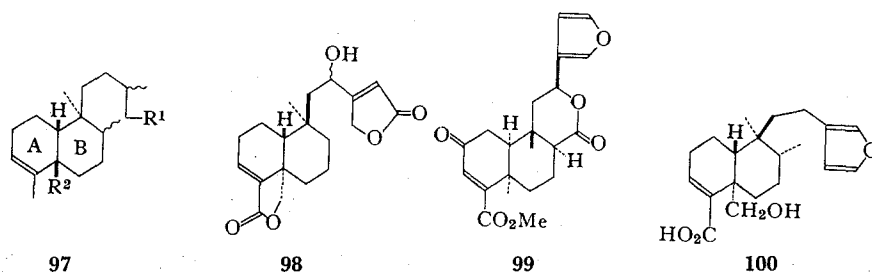
#### IV. CLERODANE DERIVATIVES



*Cistus monspeliensis* was found to contain almost exclusively compounds having the skeleton **97** with a cis-junction of A and B.<sup>46)</sup>

Chloroform extraction of *Olearia heterocarpa* yielded a new diterpene dilactone, olearin. On chemical and spectroscopic evidence, the structure of olearin was elucidated. Correlation of olearin with a diterpene of the known stereochemistry defined the absolute con-

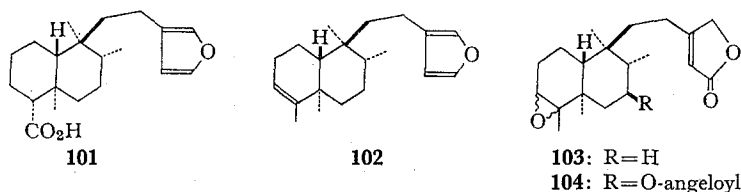




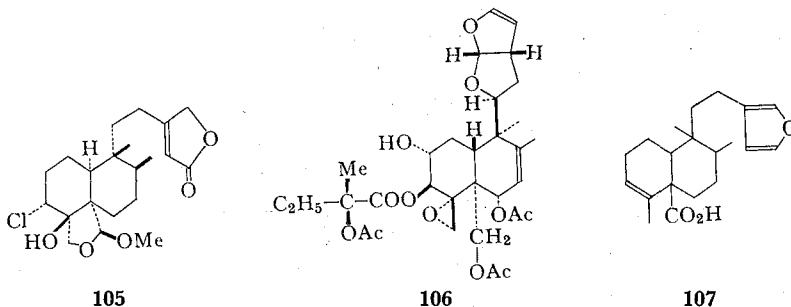
figuration at all but one center as **98**.<sup>51)</sup>

The diterpene tinophyllone was isolated from the root and bark of *Tinomiscium philippinense*. Mainly on the basis of physical data and taking into account its occurrence in a plant of the same family (Menispermaceae) as that of *Jatrorrhiza palmata* from which columbin has been isolated, its planar structure was proposed by G. Aguilar-Santos.<sup>52)</sup> An X-ray crystallographic examination confirmed the structure and determined its relative stereochemistry as **99**.<sup>53)</sup>

The structure of a diterpene carboxylic acid, hautriwaic acid, isolated from *Dodonea viscosa*, was confirmed as **100** by chemical and spectroscopic studies.<sup>54)</sup> The structures of two new diterpenoids isolated from bulbs of *Annona coriacea* were established as **101** and **102**.<sup>55)</sup> From extracts of the roots of *Solidago Shortii*, two new diterpenoids were isolated, and their structures were determined as **103** and **104**.<sup>56)</sup>



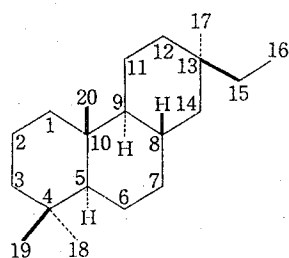
The molecular structure of the first naturally occurring chloro-diterpene, gutierolide, isolated from the alcoholic percolate of the above ground part of the annual herb, *Gutierrezia dracunculoides*, was determined as **105** by X-ray crystallographic analysis. The formula shows its absolute configuration.<sup>57)</sup>



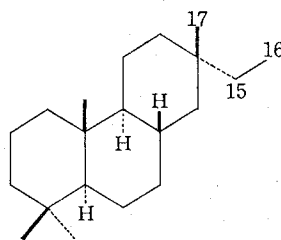
The structure of Clerodendrin A, a bitter principle of *Clerodendron tricotomum* and antifeeding repellent for the larvae of *Spodoptera littoralis*, was shown to be **106**. An X-ray analysis of the *p*-bromobenzoate chlorohydrin confirmed its structure and absolute

configuration as **106**.<sup>58)</sup> Maingayic acid, a piscicidal constituent of *Callicarpa maingyi*, was investigated, and structure **107** was proposed.<sup>59)</sup>

## V. PIMARANE AND ISOPIMARANE DERIVATIVES

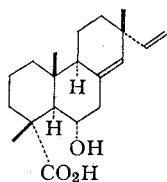
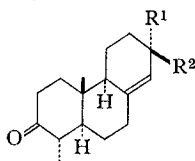
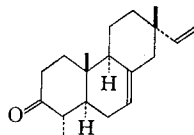


Pimarane

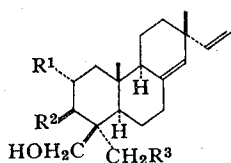
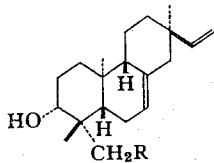
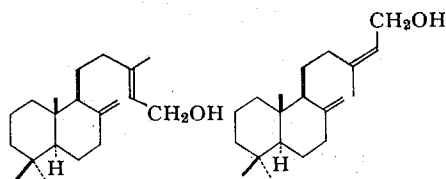


Isopimarane

A major constituent of a light petroleum extract of *Juniperus phoenicea* was sandaracopimaric acid. 6 $\alpha$ -Hydroxysandaracopimaric acid (**108**) was also isolated.<sup>45)</sup>

**108****109**: R<sup>1</sup>=Me, R<sup>2</sup>=vinyl**110**: R<sup>1</sup>=vinyl, R<sup>2</sup>=Me**111**

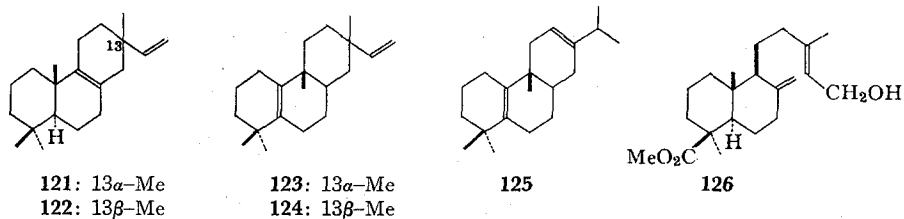
Three 19-nor-pimarane and isopimarane derivatives, **109–111**, were isolated from the light petroleum extract of the bark of *Pinus silvestris*.<sup>60)</sup> Examination of the bark of *Dacrydium colensoi* showed the presence of the diterpenoids, sandaracopimaradien-19-ol (**112**),  $-\beta$ , 19-diol (**113**),  $-\alpha$ , 18,19-triol (**114**),  $-\beta$ , 18,19-triol (**115**), and  $-\alpha$ , 3 $\beta$ , 18,19-tetraol (**116**).<sup>61)</sup>

**112**: R<sup>1</sup>=R<sup>2</sup>=R<sup>3</sup>=H**113**: R<sup>1</sup>=R<sup>3</sup>=H, R<sup>2</sup>=OH**114**: R<sup>1</sup>=R<sup>3</sup>=OH, R<sup>2</sup>=H**115**: R<sup>1</sup>=H, R<sup>2</sup>=R<sup>3</sup>=OH**116**: R<sup>1</sup>=R<sup>2</sup>=R<sup>3</sup>=OH**117**: R=OH**118**: R=H**119****120**

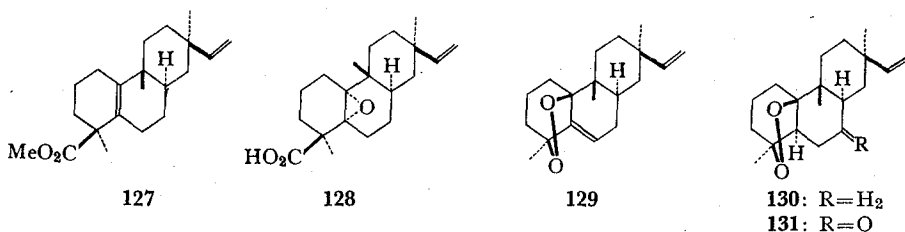
Oblongifoliol and deoxyoblongifoliol, components of *Croton oblongifolius*, were assigned the structures **117** and **118**, respectively.<sup>62)</sup>

Manool, 13-epimanool, and the related alcohols **119** and **120** were converted by acid

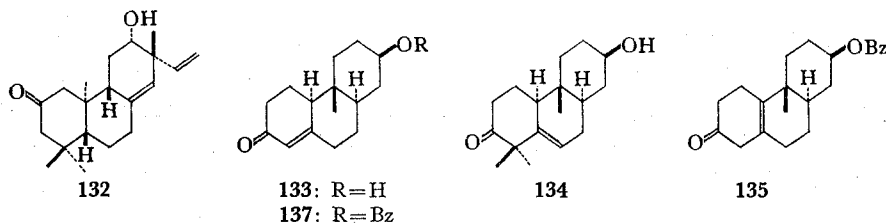
*via* pimaradienes **121** and **122** into rearranged pimaradienes **123** and **124**. Prolonged treatment with acid led to a rearranged abietadiene derivative **125**.<sup>63)</sup>



13 $\alpha$ -Methyl compound **127** which was transformed with acid from methyl isocupressate **126** was converted *via* the epoxide **128** into the unsaturated lactone **129**, and thence into deoxyrosenonolactone (**130**) and rosenonolactone (**131**).<sup>64)</sup>



The light petroleum extract of the stems of *Macaranga tanarius* yielded in addition to several other terpenoids a new diterpene ketol, macarangelonol, to which structure **132** was assigned.<sup>65)</sup>

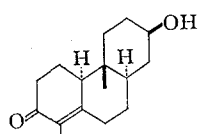


Ether extracts from the cones of *Cedrus atlantica* yielded sandaracopimaric and isopimaric acid. Those from *C. libani* yielded sandaracopimaric acid.<sup>66)\*</sup>

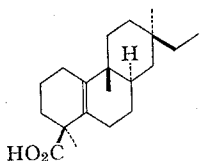
The enamine methylation of the  $\alpha\beta$ -unsaturated ketone **133** did not result in the C-methylation but in the N-methylation. The direct monomethylation of the same ketone under a controlled condition did not give a monomethylated derivative but a dimethylated  $\alpha\beta$ -unsaturated ketone **134**. However, when the  $\beta\gamma$ -unsaturated ketone **135** was methylated under a controlled condition, the expected monomethylated  $\alpha\beta$ -unsaturated ketone **136** was obtained. In this connection, the deconjugation of the  $\alpha\beta$ -unsaturated ketone **137** with trichloroacetic anhydride was also studied.<sup>67)</sup>

Rosein III, a metabolite of *Trichothecium roseum*, was converted into **138**, and also more directly to a mixture of rosenonolactone dihydro derivative (**140**) and isorosenono-

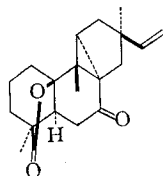
\* See also section VI.



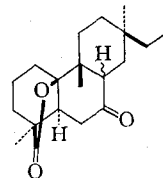
136



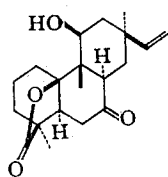
138



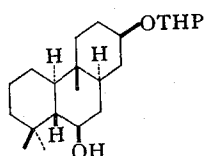
139

140: 8 $\alpha$ -H  
141: 8 $\beta$ -H

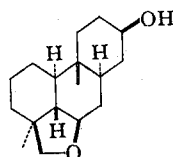
lactone dihydro derivative (**141**) *via* a novel cyclopropane intermediate (**139**). These correlations of rosein III with rosenonolactone in association with the spectroscopic evidences of derivatives substantiated its structure and absolute configuration as 11- $\beta$ -hydroxyrosenonolactone (**142**).<sup>68,69</sup> The conformation of isorosein III, a C-8 isomer of rosein III, was also clarified.



142

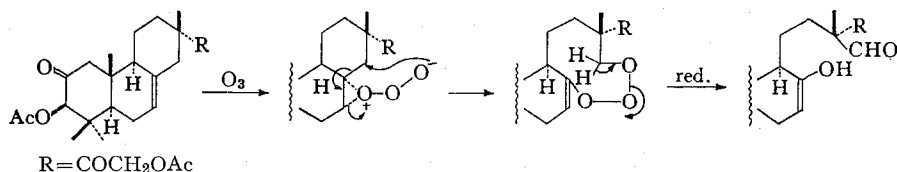


143



144

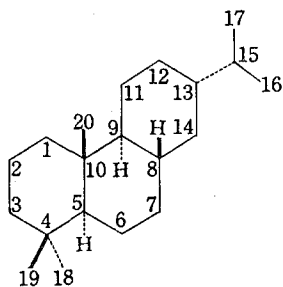
Certain "abnormal" ozonolyses, including those of several isopimarane derivatives, were explained in terms of the rearrangement of the peroxyepoxide as shown in Scheme 2.<sup>70</sup>



Scheme 2

Potential intermediates for the syntheses of rosenonolactone type diterpenoids were prepared. Compound **143** was subjected to the reaction with lead tetraacetate and iodine followed by acid hydrolysis to give ether **144**.<sup>71)</sup>

## VI. ABIETANE DERIVATIVES



Abietane

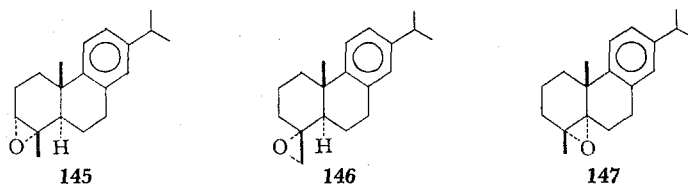
The reactions of boron trifluoride and dimethyl sulfoxide on the 3 $\alpha$ ,4 $\alpha$ -epoxy- (**145**), 4 $\alpha$ ,19-epoxy- (**146**) and 4 $\alpha$ ,5 $\alpha$ -epoxy- (**147**) derivatives of 18-norabietane-8,11,13-triene were studied.<sup>12)\*</sup>

Methyl dehydro-15-hydroxy-abietan-18-oate was isolated by column chromatography from the oleoresin of *Pinus koraiensis*.<sup>42)\*\*</sup>

Ether extracts from the cones of *Cedrus atlantica* yielded abietic, levopimaric, palustric, dehydroabietic

\* See also section II.

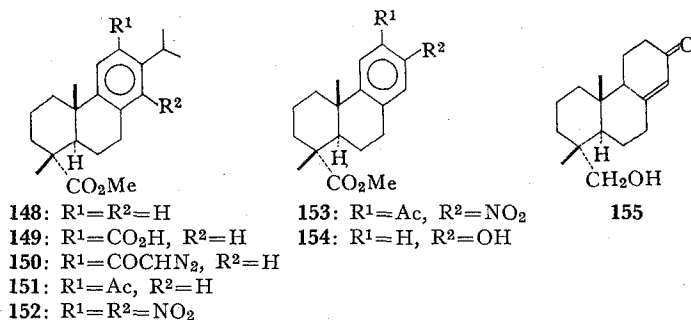
\*\* See also section III.



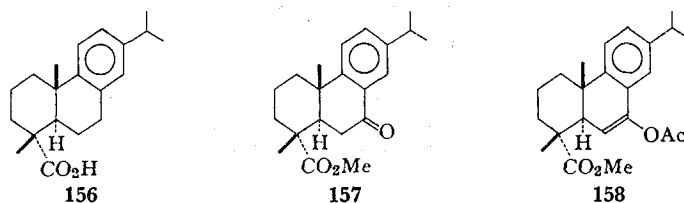
and neoabietic acids, and abieta-8,11,13-trien-7-one. The extracts of *C. libani* also yielded the same acids, abieta-8,11,13-triene, and abieta-7,13-diene.<sup>66)†</sup>

Use of *N*-lithio ethylenediamine as a dehydrogenation agent of diterpene acids was investigated and (+)-dehydroabietic acid was prepared from (–)-abietic acid.<sup>72)</sup>

Functionalization of the isopropyl group of methyl abieta-8,11,13-trien-18-oate (**148**) was achieved by intramolecular cyclizations of the 12-carboxy derivative (**149**) with lead tetraacetate and by thermolysis of the diazomethyl ketone (**150**). Nitration of methyl 12-acetylabieta-8,11,13-trien-18-oate (**151**) gave the products **152** and **153**, arising from nitrodeacylation and nitrodealkylation reactions, respectively. The nitro ketone **153** was converted into methyl 13-hydroxypodocarpa-8,11,13-trien-18-oate (**154**) in 26% overall yield from the ester **148**. Birch reduction of the methyl ether of **154** afforded the enone **155**, a potentially useful intermediate for synthesis.<sup>73)</sup>



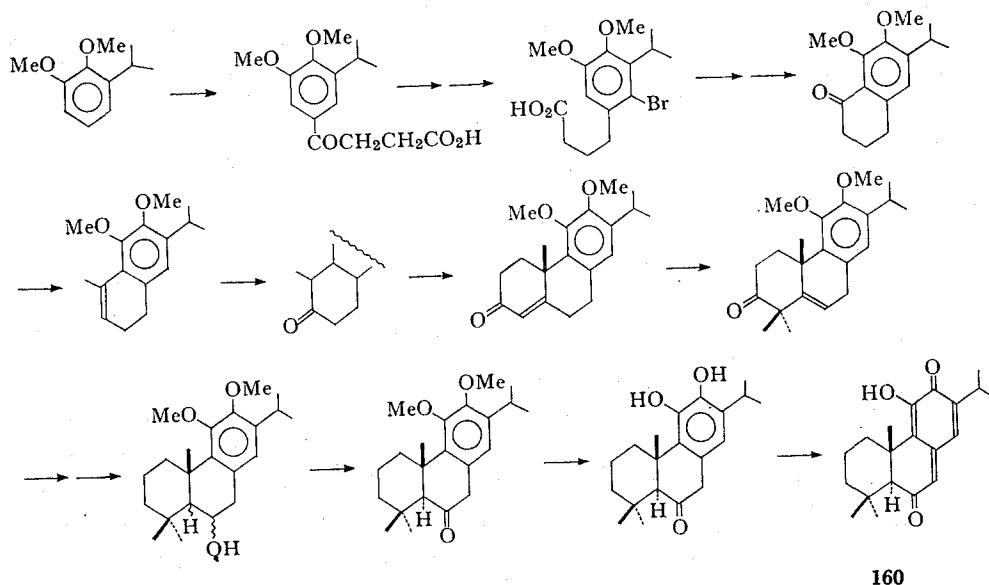
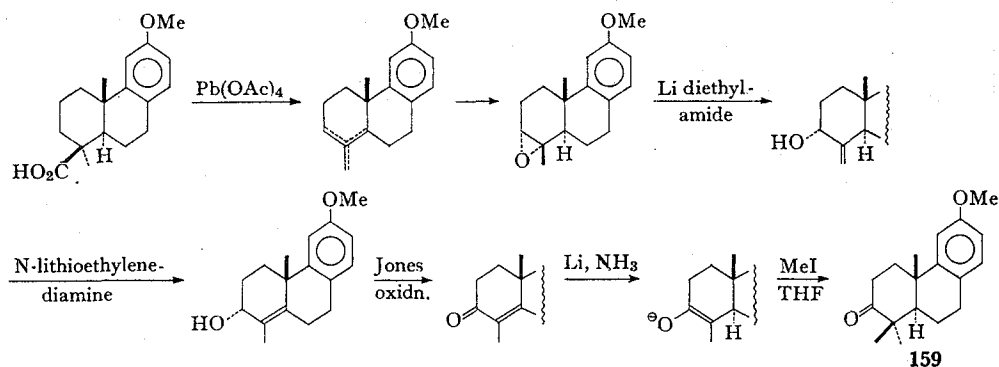
The preparation of 6-oxygenated derivatives of abieta-8,11,13-trien-18-oic acid, that is, dehydroabietic acid (**156**) was developed by peracid oxidation of the enol acetate **158** derived from the C-7 ketone **157**.<sup>74)</sup>



A synthesis of (+)-hinokione methyl ether (**159**) was carried out as shown in Scheme 3.<sup>75)</sup>

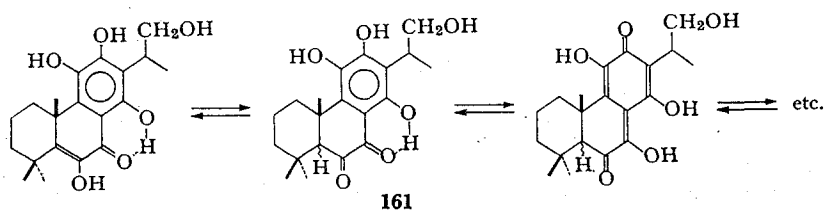
The total synthesis of *rac*-taxodione, (**160**) a tumor inhibitor, was done through the steps shown in Scheme 4.<sup>76)</sup>

† See also section V.

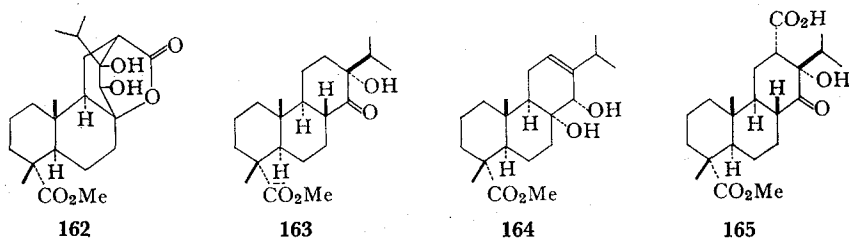


Methyl 12-chlorosulfonyl-dehydroabietate was prepared by treating methyl dehydroabietate in carbon tetrachloride with chlorosulfonic acid at  $-5^{\circ}$ .<sup>77)</sup> The thermal behavior of methyl dehydroabietate at  $600-800^{\circ}$  was investigated.<sup>78)</sup> Methyl 12-acetyldehydroabietate was converted into some derivatives.<sup>79)</sup> Dehydroabietic acid was converted to dehydroabietyl nitrile, dehydroabietylamine, and their derivatives.<sup>80)</sup>

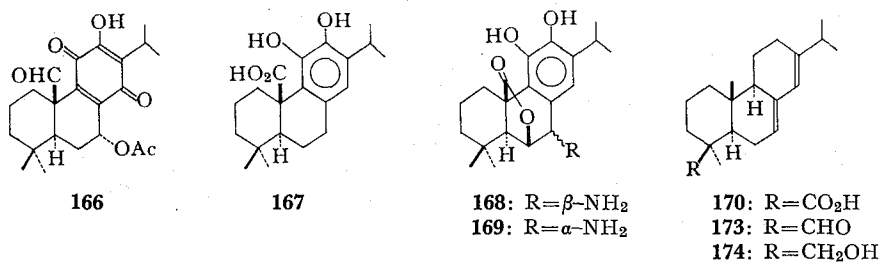
Structure of coleon C, a new yellow diterpenoid hydroquinone, isolated from the leaves and inflorescences of *Coleus aquaticus* was elucidated as **161**.<sup>81)</sup>



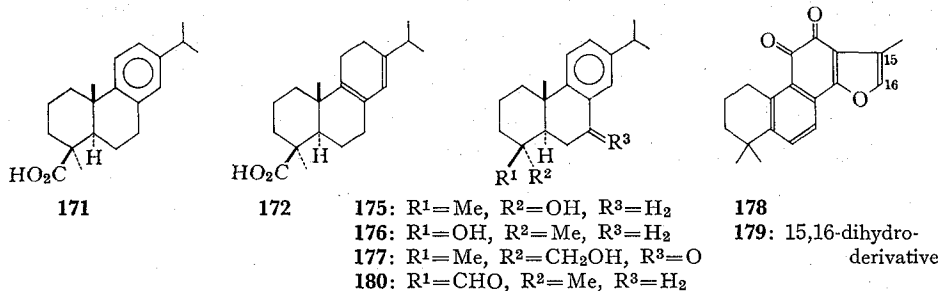
Nitration of methyl dehydroabietate by fuming nitric acid in acetic anhydride gave 27% of 14-nitro- and 47% of 12-nitroderivatives.<sup>82)</sup> Pyrolysis of a dihydroxylactone **162** gave **163** or **164**. Decarboxylation of **165** also gave **163**. These unusually facile decarboxylations were discussed.<sup>83)</sup>



Dehydroabietane was isolated from the oleoresin of *Pinus pallasiana*.<sup>84)</sup> The structure of nemorone isolated from *Salvia nemorosa* roots was determined as **166**.<sup>85)</sup>

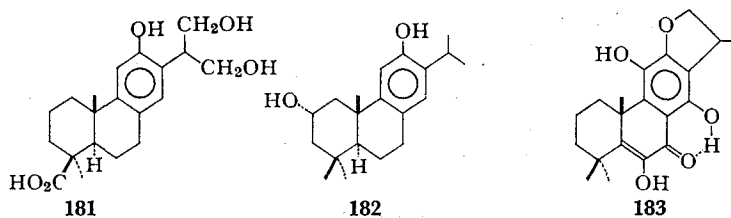


Derivatives of dehydroabietic acid with alkaloids salsolidine and cytisine were investigated.<sup>86)</sup> The main terpene component (**167**) of *Rosmarinus officinalis* gave in the presence of ammonia a mixture of rosmarinine (**168**) and isorosmaricine (**169**). Chemical transformations and NMR studies confirmed their structure and stereochemistry as shown.<sup>87)</sup> As the minor constituents of *Juniperus phoenicea*, 4-epi-abietic (**170**), 4-epi-dehydroabietic acid (**171**), 4-epi-palustic acid (**172**), 4-epi-abietal (**173**), and acid 4-epi-abietol (**174**) were isolated.<sup>88)</sup> 18-(**175**) and 19-Norabiet-8,11,13-trien-4-ol (**176**) and 18-hydroxy-8,11,13-abietatrien-7-one (**177**) were isolated from *Pinus banksiana*. In *Pinus monticola*, the presence of three 19-norabietateraenes was recognized.<sup>89)</sup>

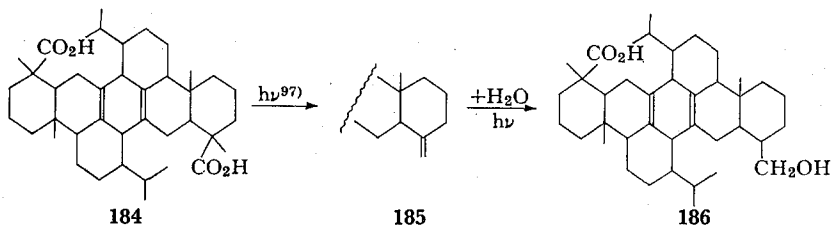


Syntheses of tanshinone-II (**178**) and cryptotanshinone (**179**) were carried out through fourteen steps of reactions from 1,2,4-trimethoxybenzene.<sup>90)</sup> Preparation of dehydroabietic acid from rosin was reported.<sup>91)</sup>

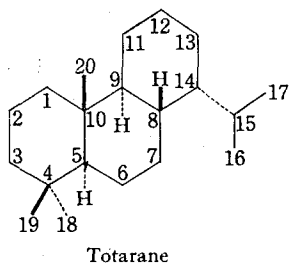
Chemical conversion of dehydroabietic acid into 4-epi-dehydroabietic acid (**171**) via 4-epi-dehydroabietal (**180**) was accomplished.<sup>92)</sup> The structure of pododacric acid isolated from heartwoods of *Podocarpus dactyloides* and *P. totara* was determined as **181**.<sup>93)</sup> A new diterpenoid phenol, salviol, was isolated from *Salvia miltiorrhiza* and its structure was determined as **182**.<sup>94)</sup>



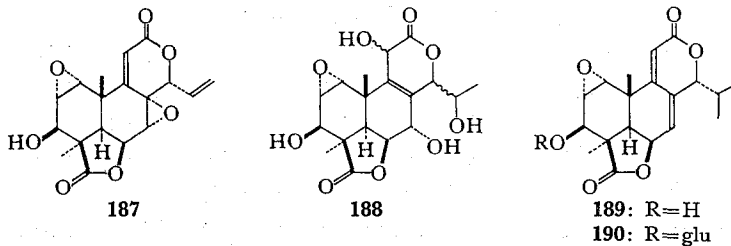
Structure **183** was assigned to lycopanol, a yellow hydroquinone diterpenoid isolated from *Lycopodium lucidulum*.<sup>95)</sup> The UV-irradiation to "Kolophonium" which was mainly consisted of abietic acid provided evidence for its dimerization into diabetic acid (**184**) and conversion of the latter into diabetolic acid (**186**), the monomer of polyester succinite. Thus, a sequence of three chemical conversions which abietic acid must encounter during formation of succinite was clarified as follows: 1) dimerization of abietic acid into diabetic acid (**184**); 2) transformation of **184** into diabetenic acid (**185**); 3) transformation of **185** into **186**.<sup>96)</sup>



## VII. TOTARANE DERIVATIVES

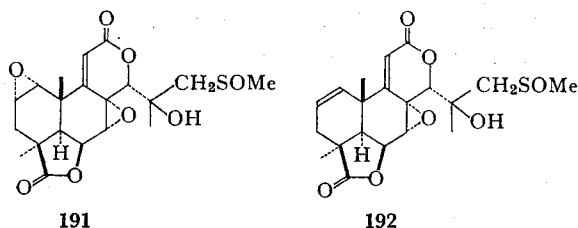


The structures **187** and **188** were suggested for inumakilactones B and C, which were isolated from the seeds of *Podocarpus macrophyllus*, respectively.<sup>98)</sup> Structures, **189** and **190**, were established, respectively, for ponalactone A and its glucoside isolated from the leaves of *Podocarpus nakaii*. Both compounds exhibited plant growth inhibitory activities.<sup>99)</sup>

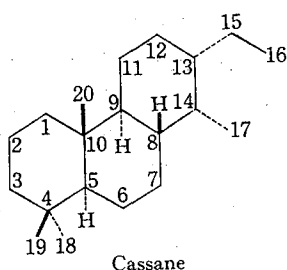




The structures of podolactones C and D isolated from *Podocarpus neriifolius* were shown to be **191** and **192** respectively.<sup>100)</sup>

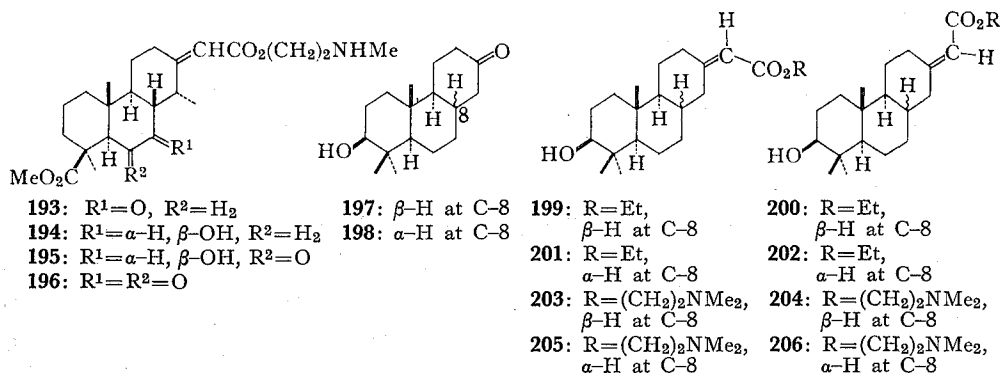


### VIII. CASSANE DERIVATIVES



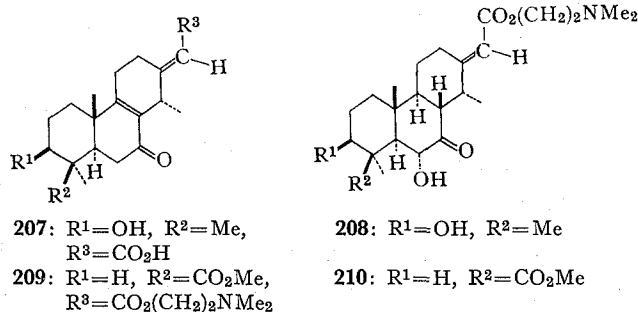
From the bark of *Erythrophleum guineense*, an alkaloid norcassamine (**193**) was isolated as the main product.<sup>101)</sup> The bark also contained norcassamidine (**194**), which was proved to be identical with erythrophleine. The originally ascribed structure was now revised. The structures of two minor alkaloids, norerythrosuamine (**195**) and dehydro-norerythrosuamine (**196**) were clarified with the aid of mass spectrometry.

"Muawin", originally regarded to be a single compound was shown to be a mixture of these alkaloids, hence the name must be canceled.<sup>101)</sup>

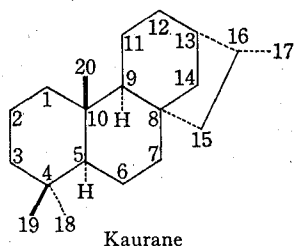


Reaction of tricyclic ketones **197** and **198** with triethyl phosphonoacetate, respectively, was investigated. The products were separated into the uniform racemic isomers **199** and **200**, **201**, and **202**, respectively. Transesterification of these compounds gave the corresponding 2-dimethylaminoethyl esters *i.e.* **203**, **204**, **205**, and **206**.<sup>102)</sup> The structures of the four isomers *i.e.* 3-oxo-derivatives of **199**, **200**, **201**, and **202** were confirmed by detailed NMR investigations.<sup>103)</sup> Catalytic hydrogenation of 3-dehydro-derivatives (3-ketones) of **199** and **200** gave 13α and 13β-ethoxycarbonylmethyl derivatives, which were separated.<sup>104)</sup> 8-Dehydrocassaic acid (**207**) was isolated by hydrolysis of impure cassaine preparations, which indicated the original existence of 6-hydroxycassaine (**208**).

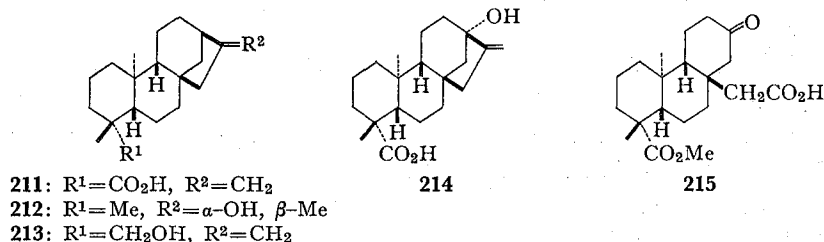
That 8-dehydrocassamine (**209**) was prepared from erythrophleguine (**210**) supported this.<sup>105)</sup>



### IX. KAURANE DERIVATIVES

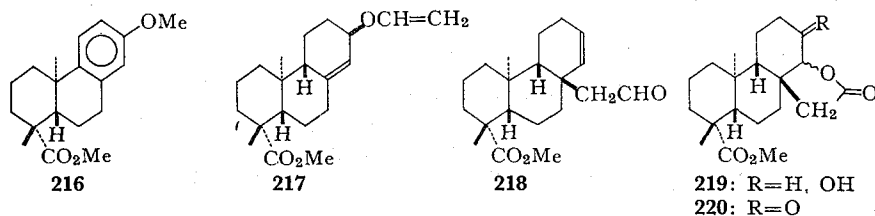


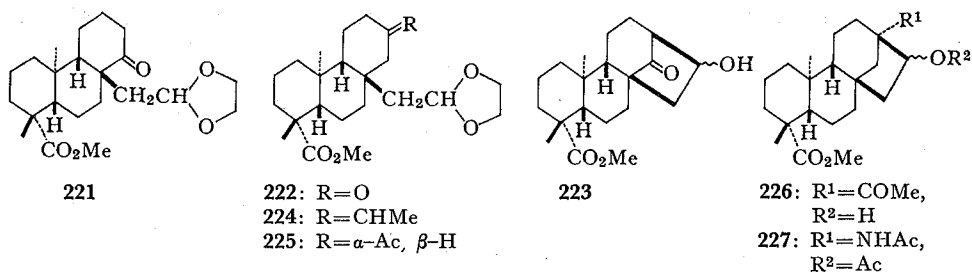
From the oleoresin of *Capaifera longsdorffii*, *ent*-16-kauran-19-oic acid (**211**) and *ent*-kauran-19-oic acid were isolated.<sup>43)</sup> From extracts of the roots of *Solidago Shortii*, *ent*-16-kauran-19-oic acid was isolated.<sup>56)</sup> *ent*-16 $\beta$ -Hydroxykaurane (**212**) was shown to be the main component of the white covering on the moss *Saelania glaucescens*.<sup>106)</sup> The occurrence of *ent*-16-kauran-19-oic acid (**211**) and *ent*-16-kauran-19-ol (**213**) in the



Australian member of the Compositae family *Abrotanella nivigena* was reported.<sup>107)</sup>

Total syntheses of *rac*-steviol (**214**) and *rac*-16-kauran-19-oic acid (**211**) were accomplished.<sup>108)</sup> A synthesis of methyl *rac*-8 $\alpha$ -carboxymethylpodocarpan-13-on-19-oate (**215**), a degradation product of steviol, was also done. From the known starting material (**216**),<sup>109)</sup> aldehyde **218** was synthesized *via* vinyl ether **217**. The compound **215** was synthesized from **218** *via* **219** and **220**. The aldehyde **218** was converted into ketones **221** and **222**. The minor product **221** was transformed into a tetracyclic compound





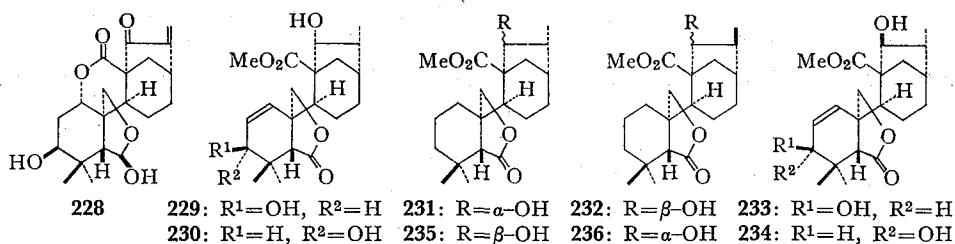
**223**, which was converted into *rac*-16-kauren-19-oic acid (**211**). On the other hand, the major ketone **222** was subjected to the Wittig reaction to give olefin **224**, which was cyclized into **226** *via* **225**. The acetyl group at C-13 in **226** was transformed to a hydroxy group *via* **227** prepared using the Beckmann rearrangement. The subsequent Jones oxidation, Wittig reaction, and hydrolysis gave *rac*-steviol (**214**).<sup>108)</sup>

The mass spectra of *ent*-16-kaurene, *ent*-16-kaurene-12, 18-diol, and *ent*-kaurane-12, 18-diol were investigated and their fragmentation patterns were discussed.<sup>110)</sup> *ent*-16-Kauren-18-oic acid, *ent*-kauran-18-oic acid and their 7- or 12-oxo derivatives were also investigated mass spectrometrically.<sup>111)</sup> An additional report on the mass spectra of *ent*-16-kaurene-15,18-diol and its derivatives was published.<sup>112)</sup>

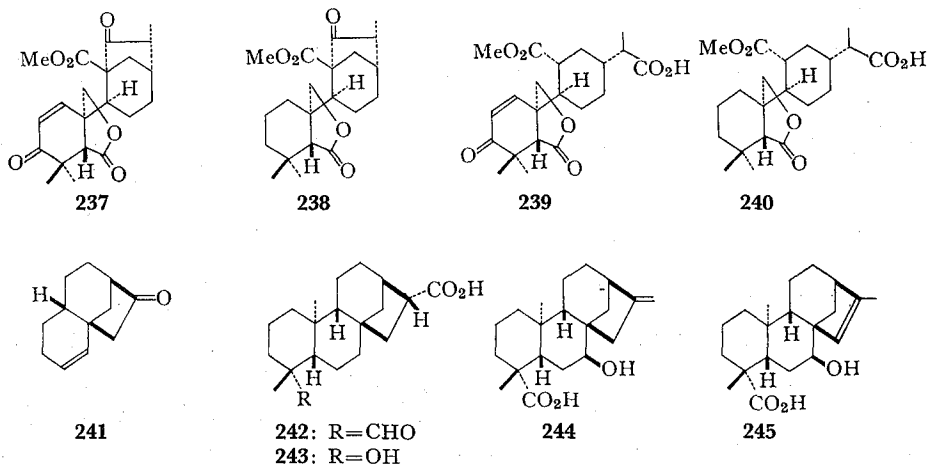
In leaf-extracts of *Rhododendron* species, the contents of grayanotoxin-I were determined by a German group.<sup>113)</sup> According to the report, a suggestion that the other grayanotoxins *i.e.* grayanotoxin-II to -VIII were not likely to be naturally occurring compounds but artifacts was provided on the basis of the thin layer chromatographic investigations.

*ent*-17-Hydroxy-15-kauren-19-oic acid was isolated from *Enhydra fluctuans* and characterized.<sup>114)</sup>

A full paper on a common stereoelectronic requirement which was recognized in epimerizations and *retro*-Dieckmann-type cleavages of some diterpene alcohols and ketones in enmein and gibberellin series was published by us.<sup>115)</sup> A stereoelectronic factor controlling epimerisations of the C-15 alcohols **229**–**232** derived from enmein (**228**), which have a *cis*-relationship between the 15-hydroxy and 16-methyl groups, into the corresponding *trans*-alcohols (**233**)–(**236**) also operated in the *retro*-Dieckmann-type cleavage of the related C-15 ketones **237** and **238** to give the carboxylic acids **239** and **240**. The mechanism of these reactions were discussed.<sup>115)</sup>



A stereoselective synthesis of *rac*-12-oxo-7,9-ethano-*cis*- $\Delta^{1,2}$ -octalin (**241**) was accomplished.<sup>116)</sup>



The mass spectra of natural and modified kaurenolides were reported.<sup>117)</sup> From the bark of *Annona senegalensis*, *ent*-kauran-16-ol, *ent*-16-kauren-19-oic acid (211), *ent*-16-epi-kauran-19-al-17-oic acid (242), and *ent*-16-epi-19-norkauran-4 $\beta$ -ol-17-oic acid (243) were isolated.<sup>118)</sup>

[17-<sup>14</sup>C] *ent*-16-Kauren-19-oic acid was converted to several products in cell-free preparations of endosperm from immature *Echinocystis macrocarpa* seeds. One of these products was identified as *ent*-16-kauren-7 $\alpha$ -ol-19-oic acid (244). A second product was tentatively identified as *ent*-15-kauren-7 $\alpha$ -ol-19-oic acid (245). The former (244) stimulated leaf sheath growth in seedlings of the dwarf-5 mutant of *Zea mays*. Also it was convertible to gibberellin A<sub>3</sub> in *Gibberella fujikuroi* mycelial suspensions. Thus, it was suggested that 244 was a normal intermediate in gibberellin biosynthesis.<sup>119)</sup>

The resin of *Espeletia grandiflora* was shown to contain *ent*-16-kauren-19-ol (246), *ent*-16-kauren-19-al (247), *ent*-16-kaurene, and *ent*-16-kauren-19-oic acid (211).<sup>120)</sup>

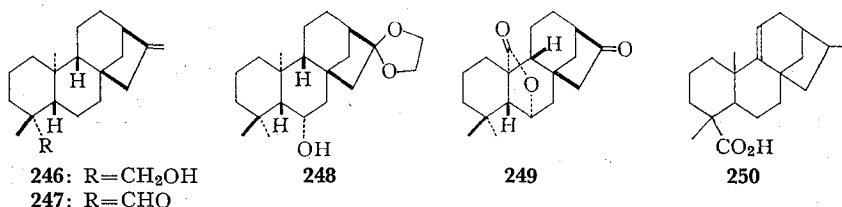
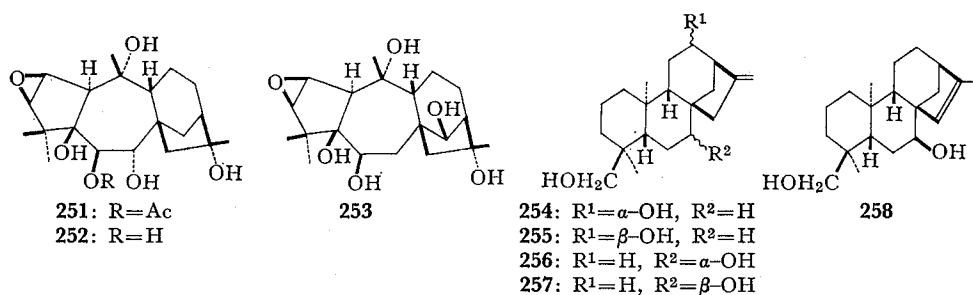


Photo-oxidation of compound 248 in the presence of iodine and lead tetraacetate followed by hydrolysis yielded the five-membered ring lactone 249.<sup>121)</sup> The mass spectra of xylopic acid (250), isolated from the light petroleum extracts of the pericarp of *Xylopia aethiopica*, and of its derivatives were investigated.<sup>122)</sup>

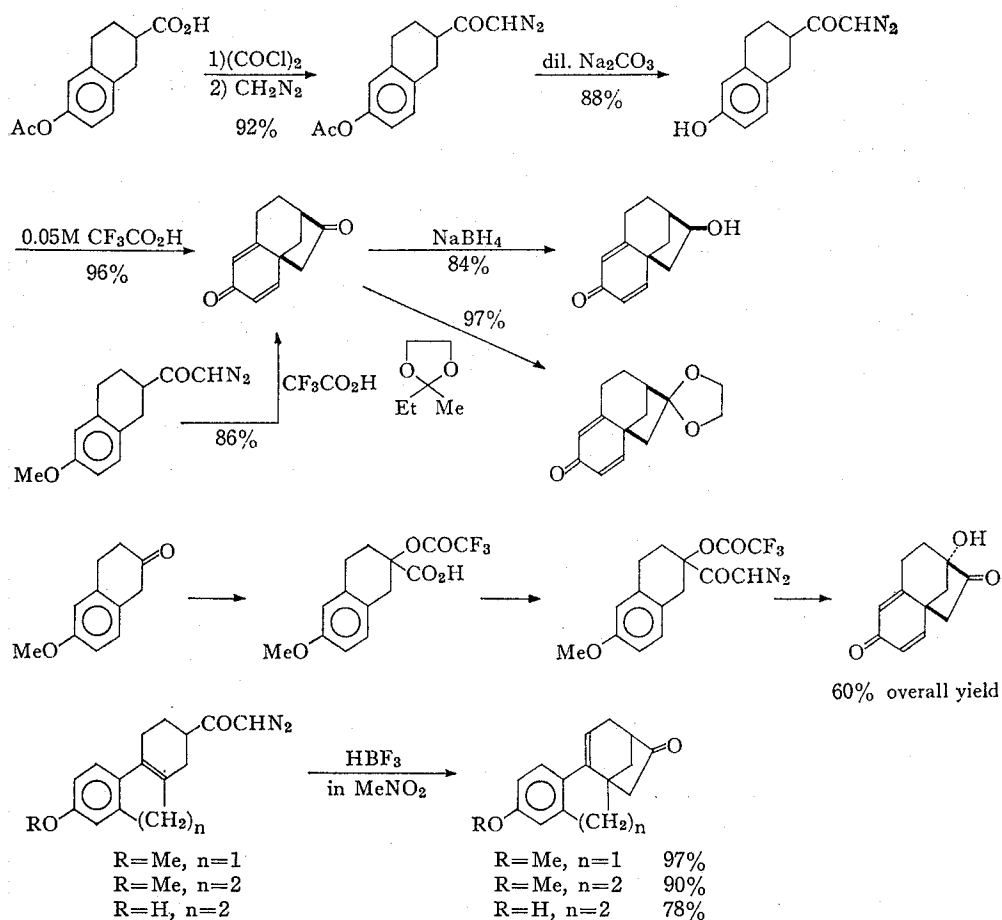
The A,B-ring juncture of lyoniol-A (251) was shown to be *trans* on the basis of the ORD investigation of the 10-keto compound derived from lyoniol-A.<sup>123)</sup> The structure of lyoniol-B was established as 252.<sup>124)</sup>

From the leaves of *Tripetaleia paniculata*, a toxic substance, rhodojaponin III (253) was isolated.<sup>125)</sup> Structures, 254 and 255,<sup>126)</sup> which had been assigned, respectively, for candicandiol and epicandicandiol isolated from *Sideritis candicans* var. *eriocephala*,



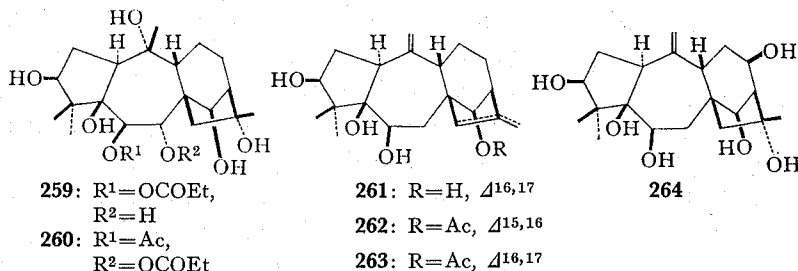
were revised to **256** and **257** by correlation with sideridiol (**258**).<sup>127)</sup>

A new annelation reaction, initiated by the protonated diazomethylcarbonyl function, was developed and a variety of intermediates for the total synthesis of tetracyclic diterpenoids were prepared as shown in Scheme 5.<sup>128)</sup>



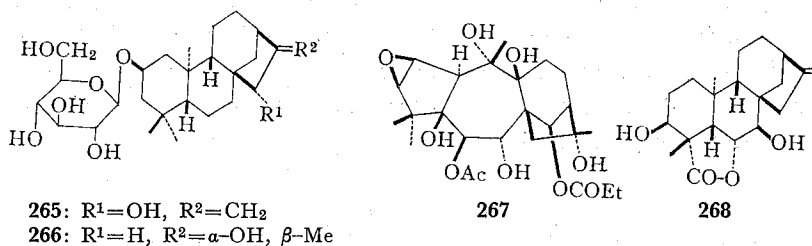
Scheme 5

The stereochemistry of asebotoxin-IV and -V, toxins of *Pieris japonica*, was determined to be **259** and **260**, respectively.<sup>129)</sup>

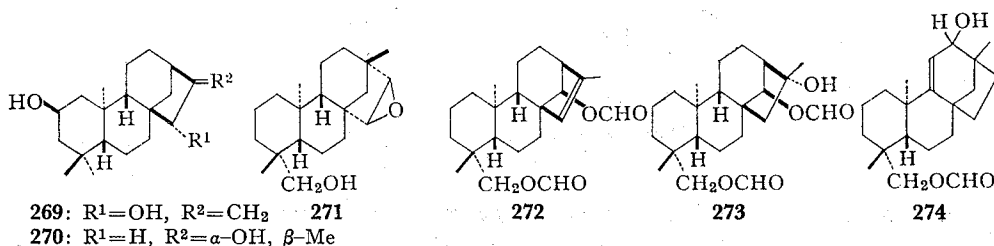


From the leaves of *Leucothoe grayana*, four novel toxins, grayanotoxin-VIII, -IX, -X, and -XI were isolated and their structures, **261**, **262**, **263**, and **264**, were determined, respectively.<sup>130)</sup>

Two new diterpenoid glucosides, creticosides A and B, were isolated from *Pteris cretica*, and structures, **265** and **266**, were assigned to A and B, respectively.<sup>131)</sup>



A new toxic diterpenoid, asebotoxin VII, was isolated from the flowers of *Pieris japonica* and structure **267** was assigned to it.<sup>132)</sup>  $3\beta,7\beta$ -Dihydroxykaurenolide (**268**) was isolated as a new metabolite from *Gibberella fujikaroi*.<sup>133)</sup> The structures of two new diterpenoids, compounds A and B, were elucidated to be **269** and **270**.<sup>134)</sup>

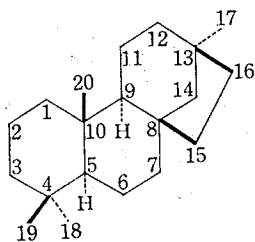


The acid-catalyzed rearrangement of a diterpenoid epoxide (**271**) was investigated. Under several different conditions, the products, **272**, **273**, and **274**, were obtained.<sup>135)</sup>

#### X. BEYERANE DERIVATIVES\*

A partial synthesis of isohibaene (**275**) starting with nezuol (**276**) was accomplished. As the key step, the intramolecular insertion reaction of a ketocarbene generated by

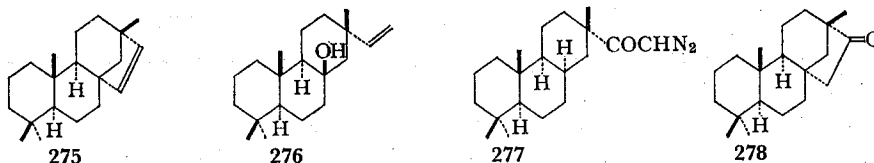
\* See also section XII (ref. 186).



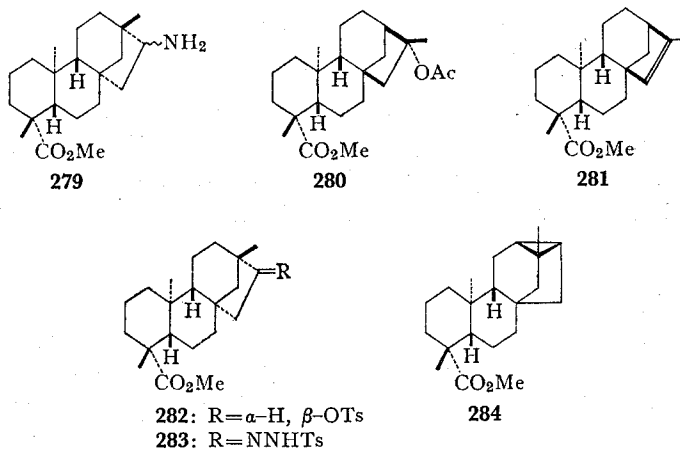
Beyerane

cuprous oxide-catalyzed decomposition of diazoketone (277) under irradiation gave ketone 278.<sup>136)</sup> It was also found that isohibaene underwent rearrangement into a mixture of phyllocladene and isophyllocladene by iodine catalytically.<sup>136)</sup>

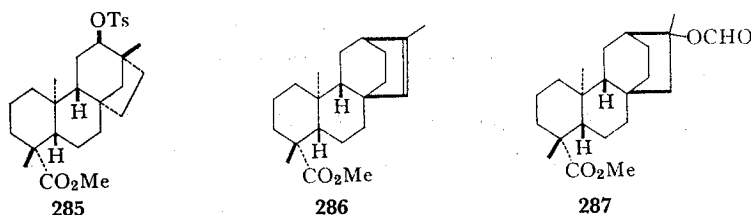
Nitrous acid deamination of methyl *ent*-16-amino-beyeran-19-oate (279) in acetic acid gave predominant rearrangement to methyl *ent*-16-acetoxykauran-19-oate



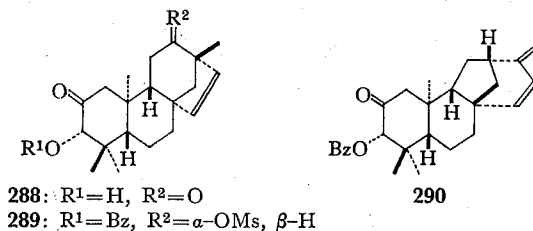
(280) accompanied by small amounts of the isomeric kaurene esters, 211 and 281. Acetolysis of tosylate 282 and decomposition of the tosylhydrazone 283 under protic conditions afforded the same rearranged, unsaturated esters, 211 and 281. In the latter reaction, methyl *ent*-13 $\alpha$ ,16-cycloatisan-19-oate (284), the C-4 epimer of methyl trachylobanoate, was also produced.<sup>137)</sup>



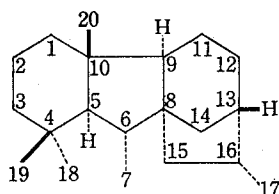
Acetolysis of tosylate 285 gave the isoatisirene ester 286 while formolysis of tosylate 285 yielded methyl *ent*-16-formyloxyatisan-19-oate (287). The various rearrangements observed formally corresponded to the ring D rearrangements suggested for the biogenesis of these tetracyclic diterpenes.<sup>137)</sup>



A tetracyclic ketol **288** was isolated as the major heartwood diterpene from *Androstachys johnsonii* and characterized. Mesylate **289** was easily converted into a new rearranged compound **290**. Thus, the latter type skeleton was suggested to occur in nature.<sup>138)</sup>



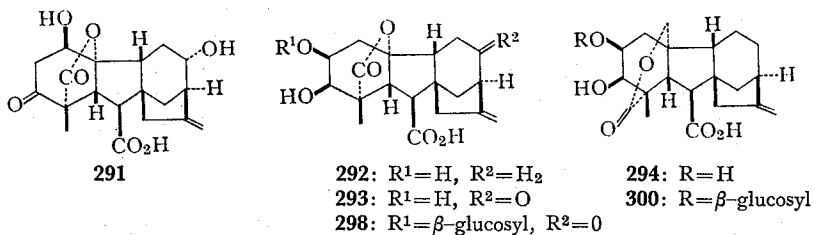
## XI. GIBBERELLANE DERIVATIVES



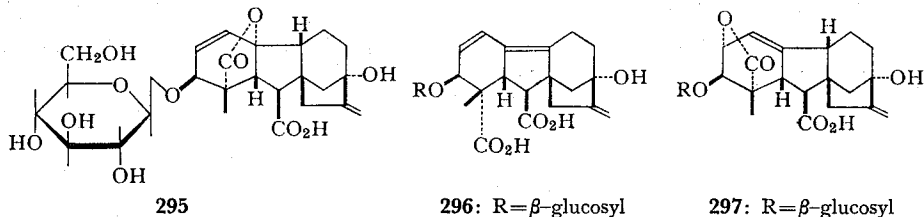
Gibberellane

The structures of the two new gibberellins,  $GA_{33}$  and  $GA_{34}$ , isolated from immature seeds of evening-glory (*Calonyction aculeatum*) were determined to be **291** and **292**, respectively.<sup>139)</sup> Gibberellin  $A_{26}$  (**293**) and  $GA_{27}$  (**294**) were isolated from Japanese morning-glory (*Pharbitis nil*) and their structures were confirmed.<sup>140)</sup>

Seven gibberellin glucosides (F-I~F-VII) were

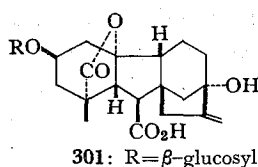
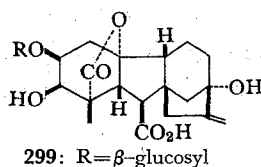


isolated from immature seeds of Japanese morning-glory. The structures were elucidated to be 3-O- $\beta$ -glucosyl- $GA_3$  (**295**), 3-O- $\beta$ -glucosyl-gibberellenic acid (**296**), 3-O- $\beta$ -glucosyl-isogibberellin  $A_3$  (**297**), 2-O- $\beta$ -glucosyl- $GA_{26}$  (**298**), 2-O- $\beta$ -glucosyl- $GA_8$  (**299**), 2-O- $\beta$ -glucosyl- $GA_{27}$  (**300**), and 2-O- $\beta$ -glucosyl- $GA_{29}$  (**301**), respectively.<sup>141)</sup>

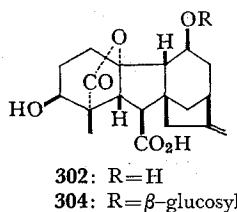


Two gibberellin-like substances were isolated from the immature pods of yellow broom (*Cytisus scoparius*). Although structures **302** and **303** were assigned to these substances, **303** was quite possible to be an artifact, so the name of gibberellin  $A_{35}$  was al-

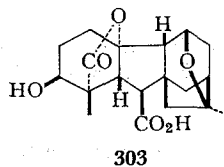




located to **302** only. Another new gibberellin glucoside was also isolated, and it was proved to be 11-O- $\beta$ -D-glucosylgibberellin A<sub>35</sub> (**304**).<sup>142)</sup>

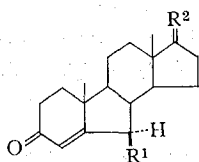


304: R =  $\beta$ -glucosyl



A review on structure, biosynthesis and effects of gibberellins was published.<sup>143)</sup>

B-Nor- $\Delta^4$ -3-ketosteroids such compounds as **305**~**310** were synthesized starting from  $\Delta^5$ -3 $\beta$ -hydroxysteroids.



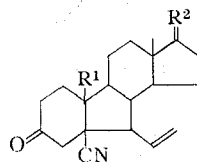
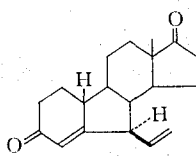
305: R<sup>1</sup> = CH<sub>2</sub>CO<sup>+</sup>, R<sup>2</sup> = O

306: R<sup>1</sup> = CH<sub>2</sub>OAc, R<sup>2</sup> = O

307: R<sup>1</sup> = CH<sub>2</sub>OH, R<sup>2</sup> = O

308: R<sup>1</sup> = CH=CH<sub>2</sub>, R<sup>2</sup> = O

309: R<sup>1</sup> = CH=CH<sub>2</sub>, R<sup>2</sup> = H<sub>2</sub>



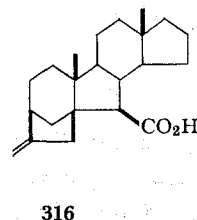
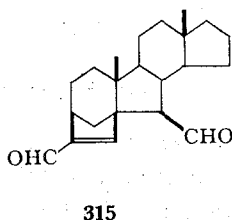
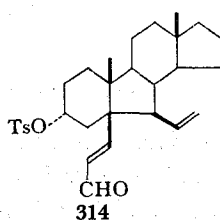
311: R<sup>1</sup> = Me, R<sup>2</sup> = O

312: R<sup>1</sup> = Me, R<sup>2</sup> = H<sub>2</sub>

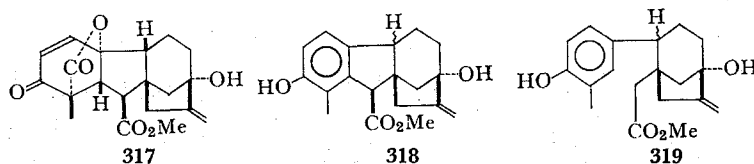
313: R<sup>1</sup> = H, R<sup>2</sup> = O

Hydrocyanation by treatment with diethylammonium cyanide was successful for only the 6 $\beta$ -vinyl derivatives (**308**, **309**, and **310**) and gave the corresponding 3-keto-5 $\beta$ -cyano-compounds (**311**, **312**, and **313**).<sup>144)</sup>

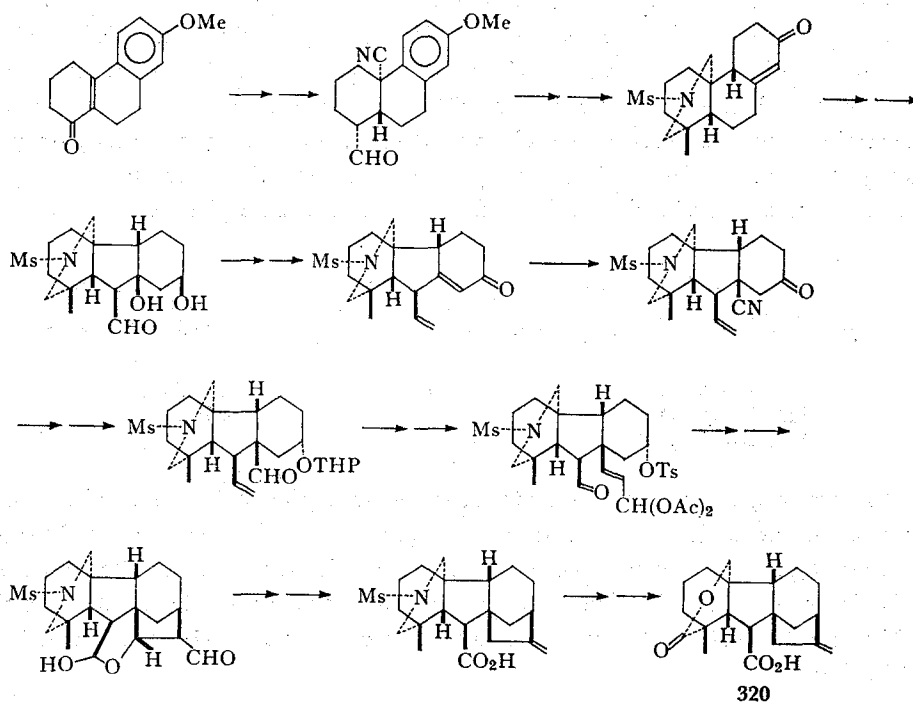
5 $\beta$ -Cyano-6 $\beta$ -vinyl-B-nor-5 $\beta$ -androstane-3-one (**312**) was transformed stereoselectively to 3 $\alpha$ -tosyloxy-5 $\beta$ -(trans- $\beta$ -formyl)vinyl-6 $\beta$ -vinyl-5 $\beta$ -androstane (**314**) by the eight-step synthesis. The latter, after selective ozonization, was subjected to a new cyclization method involving participation of 6 $\beta$ -hemiacetal function to afford 3 $\beta$ ,5 $\beta$ -etheno derivative **315**, which on subsequent oxidation and the Wolff-Kishner reduction led to modified gibberellin type compound **316**.<sup>145)</sup>



Photoconversion of **317** in *t*-butanol gave **318** in 25% yield. The photolysis of **317** in benzene gave **318** in 20% yield. Photolysis of **317** in benzyl alcohol gave **319**.<sup>146)</sup>

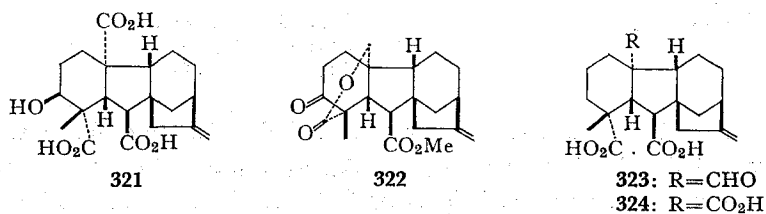


The stereocontrolled total synthesis of *rac.*-gibberellin A<sub>15</sub> (**320**) was accomplished,<sup>147b)</sup> and its full paper was published. The main route was already shown in the review in 1970 of this series, according to the communication published in 1970<sup>147a)</sup>, but the more simplified outline of the synthetic route is again shown in Scheme 6.

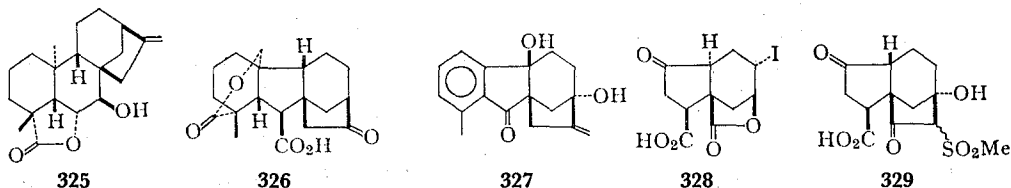


Scheme 6

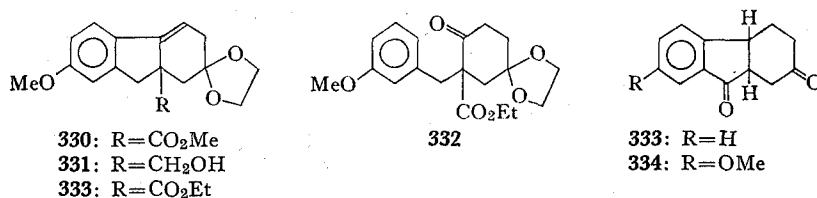
Gibberellin A<sub>12</sub> (**321**) was converted to the methyl ester (**322**) of 3-oxogibberellin A<sub>15</sub> and some related  $\delta$ -lactones.<sup>148)</sup>



Isolation, structure elucidation, and correlation with gibberellin A<sub>13</sub> and A<sub>15</sub> of two new gibberellins, A<sub>24</sub> (**323**) and A<sub>25</sub> (**324**), were reported.<sup>149)</sup> A partial synthesis of gibberellin A<sub>15</sub> norketone (**326**) from 7-hydroxykaurenolide (**325**) was accomplished.<sup>150)</sup>

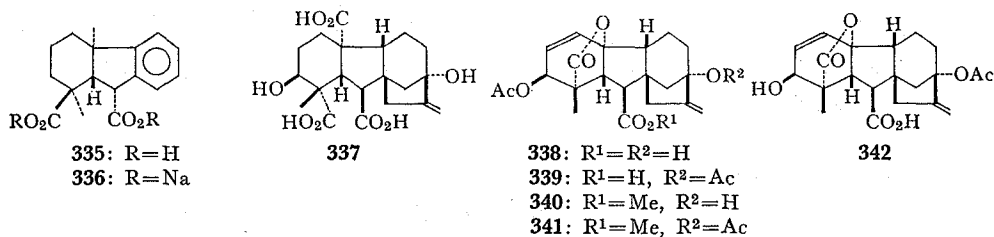


The structure **327** was assigned to a new metabolite of *Gibberella fujikuroi*.<sup>151)</sup> Studies of the synthesis of the B, C, and D rings of gibberellic acid were carried out. Compound **329** was synthesized *via* lactone **328**, but attempts to remove the extraneous D ring keto group from sulfone were unsuccessful.<sup>152)</sup> The crystal structure of **328** was shown to have the *trans* juncture between rings B and C by an X-ray analysis.<sup>153)</sup> Catalytic hydrogenation of methoxycarbonyl derivative **330** gave a *cis/trans* product ratio of 15:85, while the hydroxymethyl derivative **331** gave a ratio of 95:5. A route involving condensation of *m*-methoxybenzyl chloride with the anion of 2-ethoxycarbonyl-4,4-ethylene dioxy-cyclohexanone yielded **332** readily. This condensation and the subsequent polyphosphoric acid cyclization of **332** led to **333** in an overall yield of about 33%.<sup>154)</sup>



An efficient synthesis of hexahydrofluorene-2,9-dione (**333**) and 7-methoxyhexahydrofluorene-2,9-dione (**334**) from the appropriate phenyl pyruvic acid was published.<sup>155)</sup>

A new type of sweet compound having structure **335** was reported. Its sodium salt **336** is also very sweet. Relative sweetness of **335** to sucrose was 1300–1800, and that of **336** was 1600–2000. Their relative bitterness to caffeine was 12–18 for **335** and 12–13 for **336**.<sup>156)</sup>



A new C<sub>20</sub> gibberellin, A<sub>28</sub>, was isolated from fruits of *Lupinus luteus* and shown to have structure **337**.<sup>157)</sup> Gibberellins A<sub>1</sub>, A<sub>3</sub>, A<sub>5</sub>, A<sub>6</sub>, A<sub>8</sub>, A<sub>17</sub>, A<sub>19</sub>, and A<sub>20</sub> were identified in the seed of *Phaseolus multiflorus* by GC-MS. In the seed of *P. vulgaris* gib-

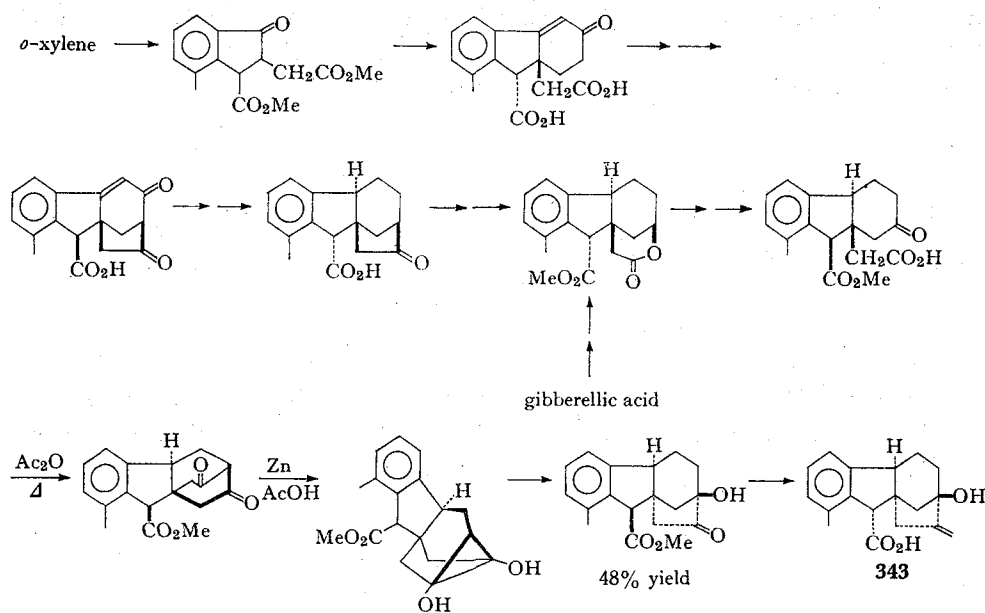
berellins A<sub>6</sub> and A<sub>8</sub> were identified by GC-MS. Gas-liquid chromatography analyses of the amounts of gibberellins in the developing seed of *P. multiflorus* and *P. vulgaris* were also reported.<sup>158)</sup>

Growth-promoting effects of gibberellins and their glucosides isolated from immature seeds of *Pharbitis nil* were compared using six bioassay systems, and the results were published.<sup>159)</sup>

The fungus *Phoma medicaginis* var. *pinodella* was shown to split off the O(3)-acetyl group of gibberellic acid acetates, **338** and **339**, and their methyl esters, **340** and **341**, without affecting O(13)-acetyl, 19,10-lactone, and methyl ester groups. Fungal deacetylation of OO(3,13)-diacetylgibberellic acid (**339**) yielded O(13)-acetylgibberellic acid (**342**), a new compound.<sup>160)</sup>

Several biological and also biochemical works on gibberellins were published.<sup>161~166)</sup> The number 3 of the lists of references for the physiologically active substances in plants was published and some gibberellins were added in this list.<sup>167)</sup>

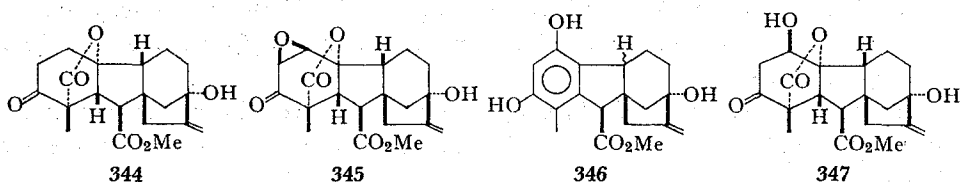
A total synthesis of *rac.* epiallogibberic acid (**343**) was accomplished employing a novel skeletal rearrangement. The outline is shown in Scheme 7.<sup>168)</sup>



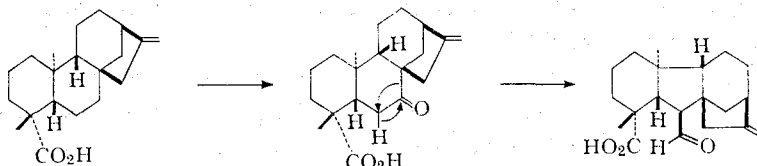
Scheme 7

The photolysis of the 3-oxo derivative (**317**) of gibberellin A<sub>3</sub> methyl ester was reported as a preliminary report and described above.<sup>146)</sup> Now, the full paper of this work was published by the same authors.<sup>169)</sup> The photolysis of **317** in *t*-butanol or benzene gave rise to the tetracyclic phenol **318** (C-9: βH), while in benzyl alcohol **317** was transformed into the tricyclic phenol **319** (C-9: βH) and the reduced ketone **344**. The epoxy ketone **345** on photolysis in dioxan afforded the resorcinol **346**; at higher temperature the latter was accompanied by the hydroxy ketone **347**.

An evidence presented by the tracer experiments suggested that the ring contraction

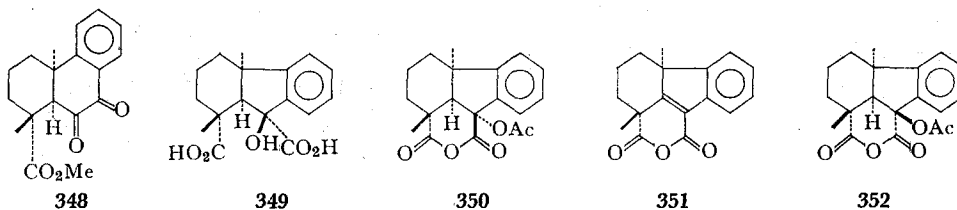


of a kauranoid diterpene to a gibberellane derivatives was accompanied by a hydrogen migration from C-6 to C-7 as shown in Scheme 8.<sup>170)</sup>

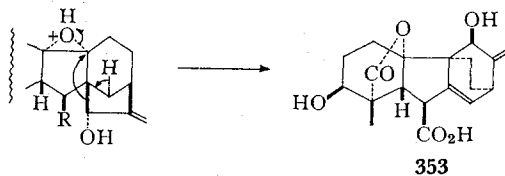


Scheme 8

Compound **348** derived from abietic acid was subjected to benzilic acid rearrangement to yield benzilic acid derivative **349**, acid anhydrides **350** and **351**. Benzilic acid **349** on acetylation gave rise to an epimerization at C-6 to yield **350**.<sup>171)</sup> These facts resulted in the revise of the previously assigned structure **352**.<sup>173)</sup>



Structure **353** including absolute configuration was assigned to the antheridium-inducing factor, antheridiogen-An, isolated from culture media of the fern *Anemia phyllitidis*. The biogenesis was suggested as shown in Scheme 9.<sup>173)</sup>

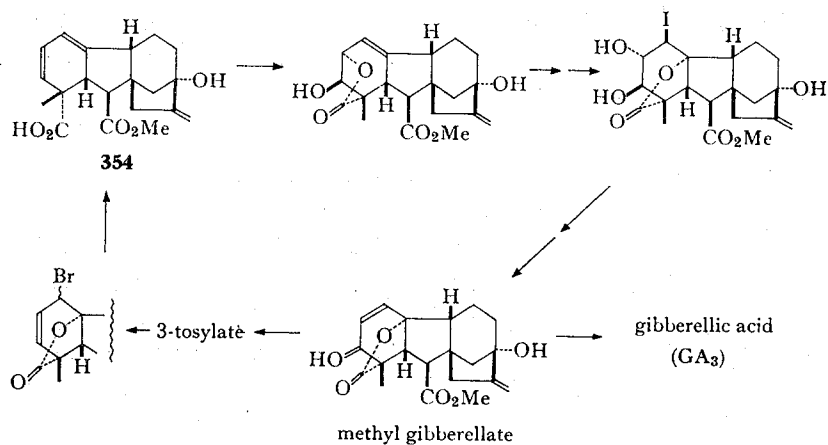


Scheme 9

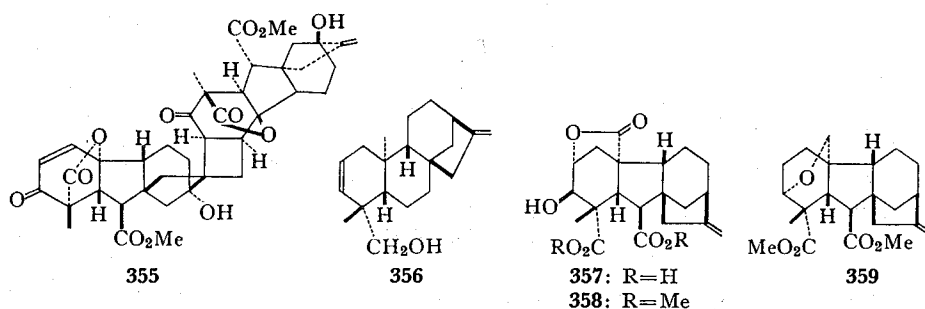
Compound **354** derived from methyl gibberellate was converted back to gibberellic acid by the following route shown in Scheme 10.<sup>174)</sup>

The enone **317** was shown to be photoreactive in solid state yielding a cyclobutane photodimer as a main product, for which structure **355** was proposed.<sup>175)</sup>

The structure of a new metabolite formed by feeding *ent*-2,16-kauradien-19-ol (**356**) to *Gibberella fujikuroi* was determined as **357** by chemical conversions of its methyl ester

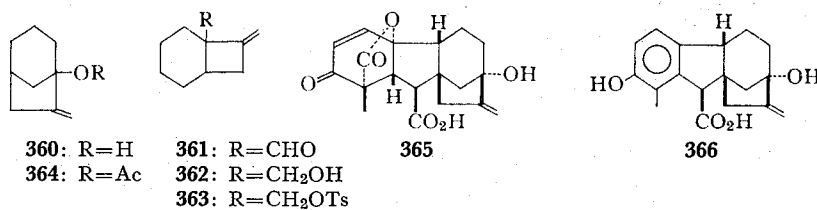


Scheme 10

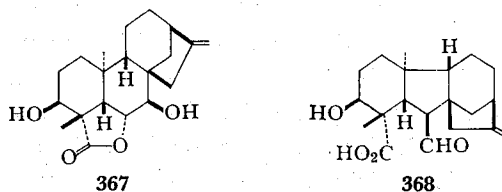


(**358**) to compound **359** *via* two routes. A bioassay against d<sub>1</sub>-maize showed a significant response which was comparable with that observed with gibberellins A<sub>5</sub>, A<sub>6</sub>, A<sub>18</sub>, and A<sub>22</sub>.<sup>176)</sup>

1-Hydroxy-7-methylene bicyclo [3.2.1.] octane (**360**), a gibberellin-steviol C/D ring model, was synthesized *via* **361**, **362**, **363**, and **364**.<sup>177)</sup>

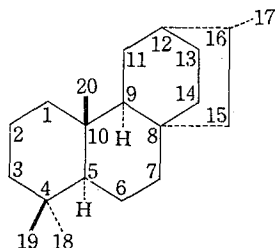


The enone **365** was also photoreactive in solid state and converted into the A-ring aromatized product **366**.<sup>178)</sup>



A partial synthesis of aldehyde **368**, a probable biosynthetic intermediate of gibberellins, from the lactone **367** isolated from the culture filtrate of *G. fujikuroi* was carried out.<sup>179)</sup>

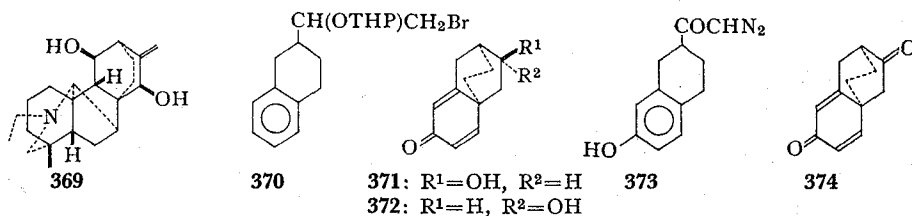
## XII. ATISANE DERIVATIVES



Atisane

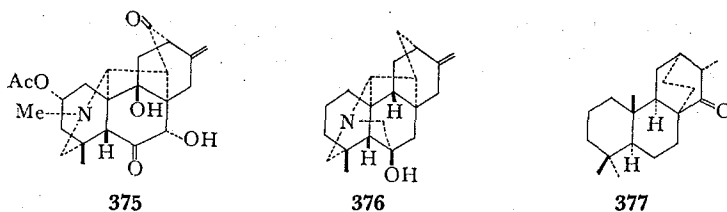
The crystal and molecular structure of denudatine was established as **369** by an X-ray analysis.<sup>180)</sup> The tricyclic dienones **371**, **372**, and **374** were prepared by the Ar<sub>1</sub>-6 cyclization of a diastereomeric mixture of **370** and of **373**.<sup>181)</sup>

The structure of an *Aconitum* alkaloid, miyaconitine, was determined by the X-ray analysis of crystals of the hydrobromide dihydrate. It was established that



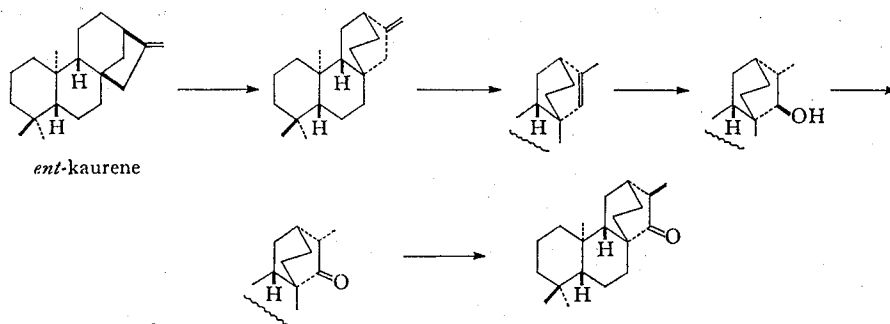
miyaconitine has structure **375** and is a novel type of *Aconitum* alkaloid.<sup>182)</sup>

The structure of spiradine A, initially isolated from the shrub *Spiraea japonica*,<sup>183)</sup> was determined as **376** by the X-ray analysis of its methiodide.<sup>184)</sup>



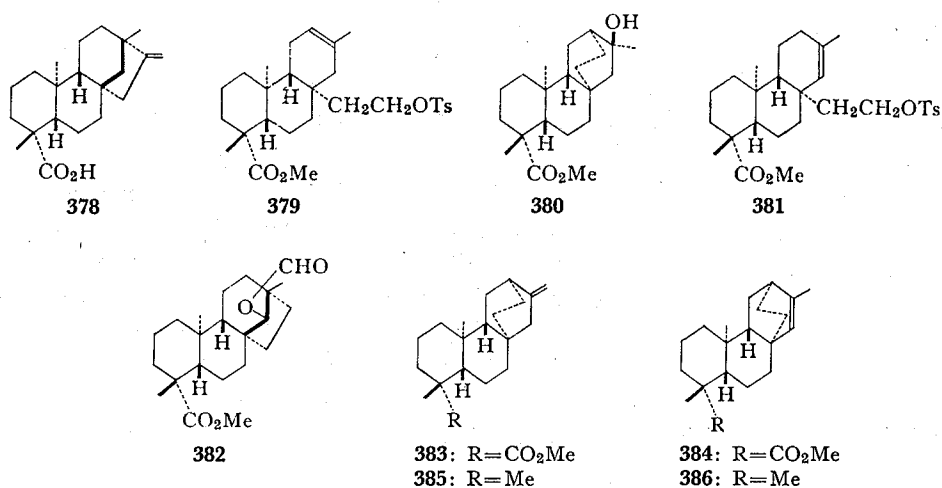
Synthesis of a neoatisiranone, the enantiomer of a ketone obtained by the acid-catalyzed rearrangement of isophyllocladene epoxide, confirmed the constitution and stereochemistry of the ketone to be **377**. The route of the synthesis of the enantiomer of **377** is shown in Scheme 11.<sup>185)</sup>

Structure modifications of isosteviol (**378**) were investigated. Various 15- and 16-substituted methyl *ent*-beyeran-19-oates were prepared by means of functional interconversion in ring D. Ring C functionalization at positions 12 and 14 was accomplished by degradation to the unsaturated tricyclic tosylate esters **379** and **381** followed by recyclization. Thus, buffered formolysis of **379** at room temperature afforded after partial hydrolysis *ent*-atisane derivative **380**. Formolysis of **381** at 80° gave *ent*-beyerane derivative **382**. Dehydration of **380** produces the exocyclic and endocyclic unsaturated

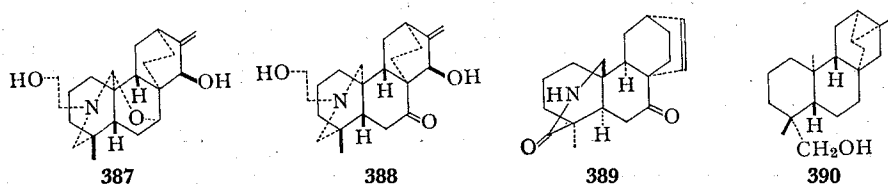


Scheme 11

esters **383** and **384** which were separately converted into atisirene (**385**) and isoatisirene (**386**).<sup>186)</sup>



A number of optically active tetracyclic intermediates possessing a carbonyl group at C-7 and a bicyclo [2.2.2] octane C,D-ring system for a synthetic approach to the diterpenoid alkaloids, ajaconine (**387**) and atidine (**388**), was synthesized from methyl O-methyl-7-ketopodocarpate. The ORD curves of these compounds provided interesting insight into the effect of C,D ring substituents on the conformation of the B-ring. A pentacyclic unsaturated ketolactam **389**, useful for further conversion to ajaconine and atidine, was synthesized.<sup>189)</sup>

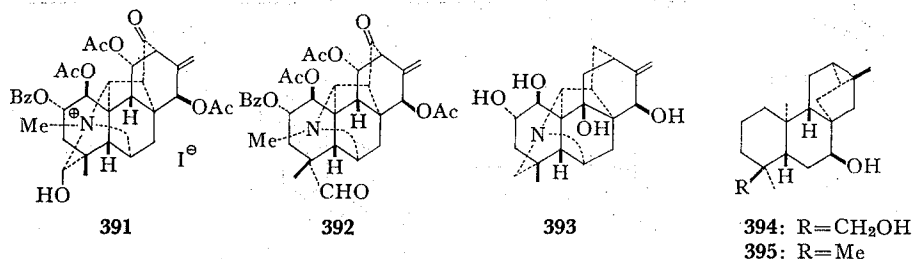


The Eu(dpm)<sub>3</sub>-shifted NMR spectrum of a new diterpene provided independent evidence for its structure **390**.<sup>188)</sup>

An X-ray crystallographic study of vakognavine hydroiodide clarified its structure



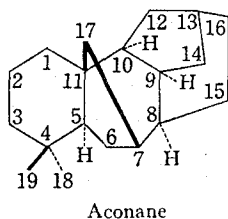
to be **391**. That vakognavine base, an alkaloid of *Aconitum palmatum*, exists as **392** was shown by the presence of an aldehyde signal in the NMR spectrum.<sup>189)</sup>



The structure of hypognavinol was established as **393** by a single crystal X-ray analysis of its methiodide.<sup>190)</sup>

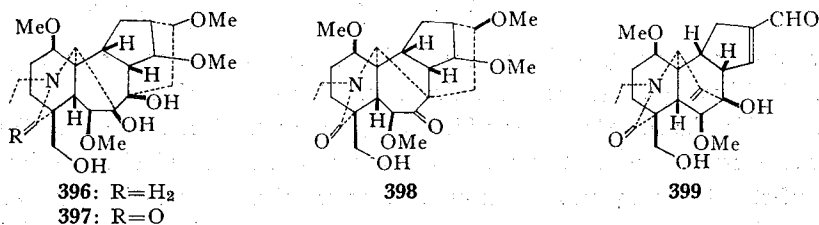
Two new diterpenes, trachinodiol (**394**) and trachinol (**395**), were isolated from *Sideritis canariensis* and characterized.<sup>191)</sup>

### XIII. ACONANE DERIVATIVES



The lactam **397** derived from lycoctonine (**396**) underwent acid-catalyzed dehydration of the *vic*-glycol system to give anhydro-oxolycoctonine (**398**). More vigorous acid treatment converted these (**397** and **398**) to lycoctamone (**399**). Proof of structure and a mechanism for the formation of this compound were presented. The analogous derivatives were also pro-

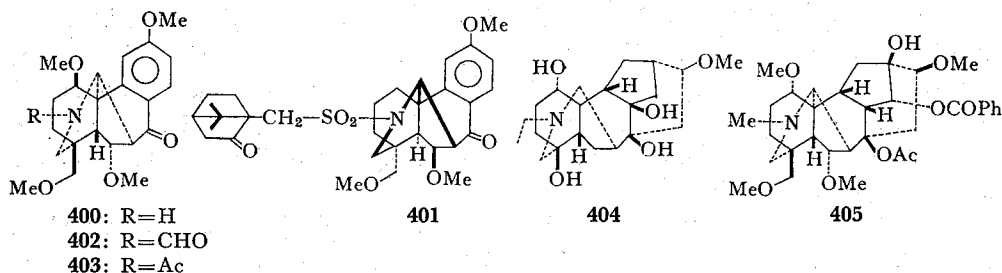
duced from other alkaloids of the lycoctonine family.<sup>192)</sup>



Resolution of the racemic relay compound synthesized as a key intermediate for the total synthesis of delphinine was accomplished. Thus, racemic compound **400** was treated with L-camphorsulfonyl chloride to yield sulfonamide **401** and optically active base **400** which was proved to be identical with the corresponding degradation product from delphinine.<sup>193)</sup>\*

The *N*-acyl group of oxonitine, an oxidation product of aconitine, was found to be a mixture of *N*-acetyl and *N*-formyl groups. It was rigorously proved that the aromatization product of oxonitine was a mixture of **402** and **403** and consequently also "oxonitine" must be a mixture of the *M*-acetyl and *N*-formyl derivatives.<sup>194)</sup>

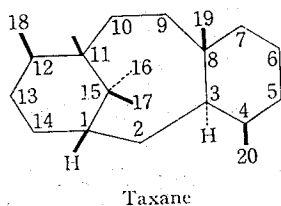
\* See also ref. 197.



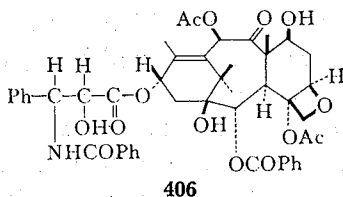
The structure **404** for an alkaloid lapaconidine separated from *Aconitum leucostomum* was proposed on the basis of chemical and spectroscopic data.<sup>195)</sup> An investigation on pyrolysis of *Aconitum* alkaloids was carried out.<sup>196)</sup>

Configuration of the ring A methoxyl group in delphinine and aconitine was reversed and thus delphinine was shown to be represented by **405**, on the basis of the X-ray crystallography of a degradation product oxalate derivative.<sup>197)</sup>

#### XIV. TAXANE DERIVATIVES

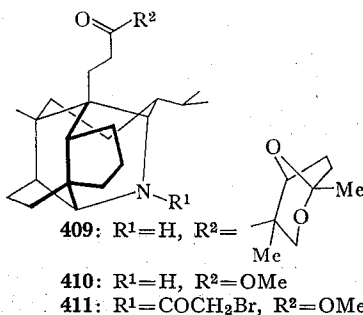
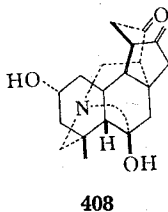
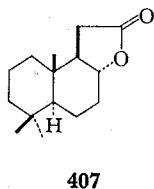


The structure of a novel compound named taxol, isolated from the stem bark of *Taxus brevifolia*, was determined as **406**. Taxol has potent antileukemic and tumor inhibitory properties and is the first compound possessing taxane ring which has been demonstrated to have such activity.<sup>198)</sup>



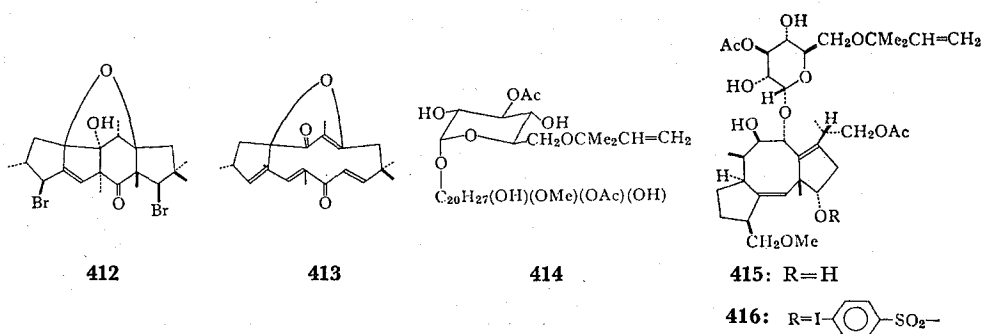
#### XV. THE OTHERS

Norambreinolide (**407**) which can be considered a degradation product of diterpenoid was isolated from cigar tobacco.<sup>198)</sup>



The X-ray crystallographic analysis of delnudine hydrochloride established the structure of the alkaloid as **408**.<sup>199)</sup> Fifty-one resin acid methyl esters (22 with abietane, 6 with pimarane, 8 with isopimarane, 8 with labdane, and 7 with miscellaneous skeletons) were purified to 99% by an appropriate combination of AgNO<sub>3</sub>-alumina column, gel permeation, and preparative gas-liquid chromatography and their NMR, IR, UV, and mass spectra recorded.<sup>200)</sup>

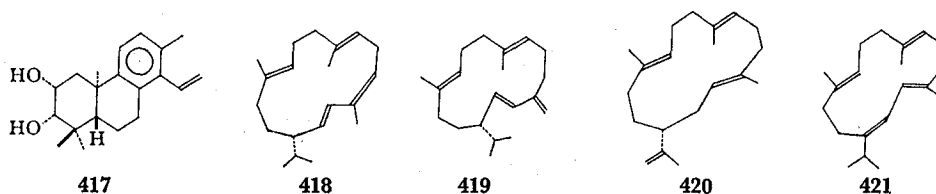
Structures including absolute configurations of new alkaloids, secodaphniphylline and methyl homosecodaphniphyllate, isolated from *Daphniphyllum macropodum*, were determined as **409** and **410**, respectively, by the X-ray analysis of methyl *N*-bromoacetylhomosecodaphniphyllate (**411**).<sup>201)</sup> Crystal structure of jatrophone dihydrobromide was established as **412** and the original jatrophone as **413**.<sup>202)</sup>



Fusicoccin, a phytotoxic glycoside metabolite by *Fusicoccum amygdali*, was shown to be **414**.<sup>203)</sup> Combining X-ray crystallography of the aglycone derivative with chemical evidence afforded the complete structure **415** of fusicoccin.<sup>204)</sup> Independently, the X-ray crystallography of *p*-iodobenzenesulfonate was carried out and the structure **416** was established for fusicoccin A *p*-iodobenzenesulfonate.<sup>205)</sup>

The CD of some tertiary carboxylic acids was examined over the range  $-10$  to  $-160^\circ$ . The percentage changes in  $\Delta\epsilon$  were ca. 25% for diterpene-4 $\beta$ (axial)-carboxylic acids and very small for diterpene-4 $\alpha$ (equatorial) carboxylic acids. The examined compounds are 18- and 19-oic acids or their methyl esters of podocarpane, labdane, abietane, cassane, and kaurane.<sup>206)</sup>

Detailed evidence supported the structure **417** for cleistanthol obtained from heartwood of *Cleistanthus schlechteri* var. *schlechteri*.<sup>207)</sup>



A method for preparing <sup>3</sup>H-labeled ryanodine was published. Thus, the alkaloid was brominated, and the bromoryanodines were separated by thin layer chromatography. The bromo-derivatives were hydrogenated to give ryanodine. They were treated with

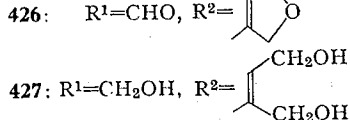
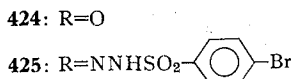
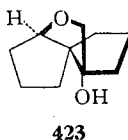
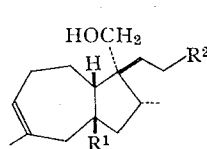
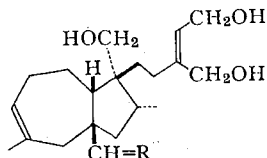
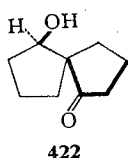
$^3\text{H}$  to yield labeled ryanodine. Isotope exchange did not occur when the labeled alkaloid was incubated in aq. media at pH 7.0 and  $30^\circ$ .<sup>208)</sup>

A short review on the structure and synthesis of diterpenes was published in Japanese.<sup>209)</sup>

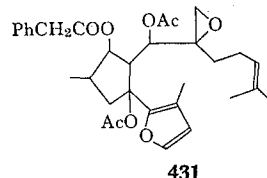
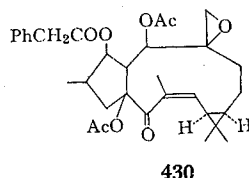
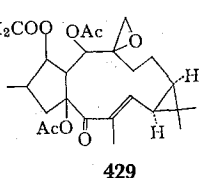
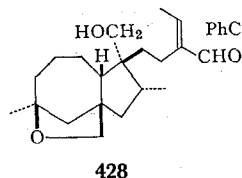
Stereochemistry of cembrene and related diterpenoids was investigated. The unconjugated double bonds in cembrene (**418**), isocembrene (**419**), and neocembrene (**420**) had the *trans* configuration; the conjugated trisubstituted double bond of cembrene the *cis* configuration. The asymmetric center of neocembrene was R. Hydrogenations of cembrene and isocembrene were also studied.<sup>210)</sup>

$\alpha$ -,  $\beta$ -, and  $\gamma$ -Pinacenes, isolated from oleoresin of *Pinus koraiensis* and *P. sibirica* by column chromatography were stereoisomers of  $\alpha$ -pinacene (**421**), which differed in the configuration of their conjugated double bonds. Isomerization of cembrene (**418**) with iodine in  $\text{CCl}_4$  gave 7%  $\alpha$ -pinacene, 45%  $\beta$ -pinacene, and 8%  $\gamma$ -pinacene.<sup>211)</sup>

Starting from compound **422**, compound **423** was synthesized, which represented the main skeleton of the ginkgolides.<sup>212)</sup>



The crystal structure of portulal *p*-bromophenylsulfonyl-hydrazone was determined by a three-dimensional X-ray analysis as **425**. Thus, the absolute structure of portulal, a plant growth regulator from *Portulaca grandiflora*, was established as **424**.<sup>213)</sup> Portulal was oxidized with active manganese dioxide to give a  $\gamma$ -lactone **426**. The aldehyde group of portulal was reduced with  $\text{LiAlH}_4$  to yield portulol (**427**), which was converted to an  $\alpha\beta$ -unsaturated aldehyde **428**. The physiological activity of these compounds was tested.<sup>214)</sup>



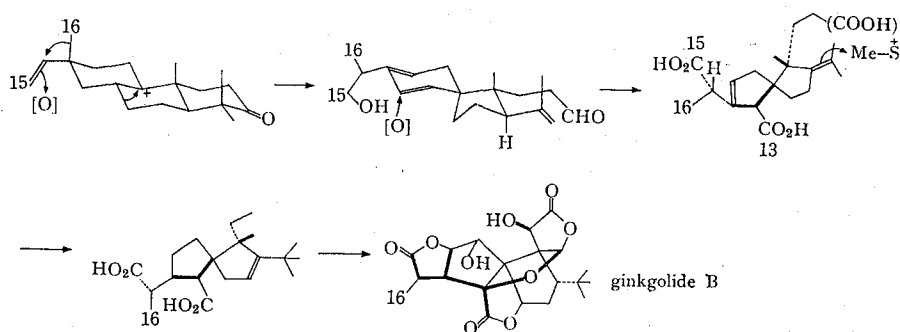
Correlation of Mills' and Brewster's rules with the Cotton effects of cyclic olefins was investigated using 74 substituted olefins including several diterpenoids having exocyclic methylene group in their molecule.<sup>215)</sup> A review of the synthesis of polyprenyl alcohols was published.<sup>216)</sup> In a review "Chemicals from plants", stevioside and steviol

are described.<sup>217)</sup>

Photochemistry of the extended conjugated system, 3-oxoprop-1-enylcyclopropane, of the diterpene, epoxylathyrol (**429**) was investigated. The system was shown to be isomerized by light to the *cis*, non-planar, enone **430**, and thence to the fragmentation product **431**, a furan.<sup>218)</sup>

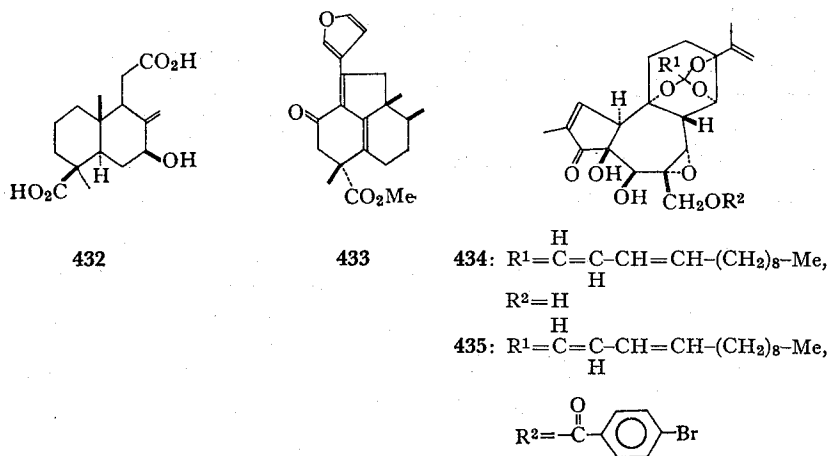
Detailed analysis of a number of exocyclic olefins showed that the sign of  $\pi \rightarrow \pi^*$  absorption can be related to absolute configuration by use of the Octant rule. As the diterpenes, *ent*-kaurene, phyllocladene, and 13(15)-abieten-18-oic acid were used for this investigation.<sup>219)</sup>

Biosynthesis of ginkgolide B in *Ginkgo biloba* was investigated, and its diterpenoid nature and the origin of the *tert*-butyl group were confirmed. The biosynthetic pathway is shown in Scheme 12.<sup>220)</sup>



Scheme 12

The third  $C_{16}$  terpenoid metabolite, LL-Z1271 $\beta$ , was isolated from the fermentations of an *Acrostalagmus* species, and characterized as **432**.<sup>221)</sup>

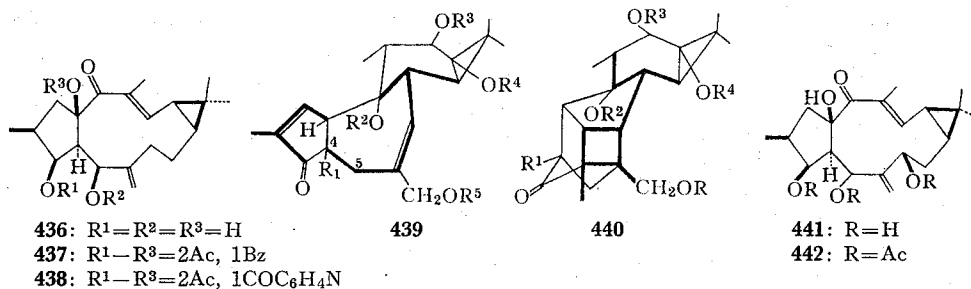


The structure of chettaphanin-II isolated from *Adenochlaena siamensis* was determined to be **433**. The stereochemistry was established by the X-ray analysis.<sup>222)</sup>

Huratoxin, a piscicidal constituent, was isolated from the sap of *Hura crepitans*.

The results of some degradations of huratoxin, coupled with other chemical and spectral data, led to the structure **434** for huratoxin, and its absolute configuration was established by X-ray analysis of *p*-bromobenzoate **435**.<sup>223,224)</sup>

A diacetate-benzoate **437** and a diacetate-nicotinoate **438** of new diterpene lathyrol **436** and a monoester of diterpene ingenol were isolated from the seed oil or latex of *Euphorbia lathyris*. The biogenesis of the diterpene from Euphorbiaceae was discussed.<sup>225)</sup>

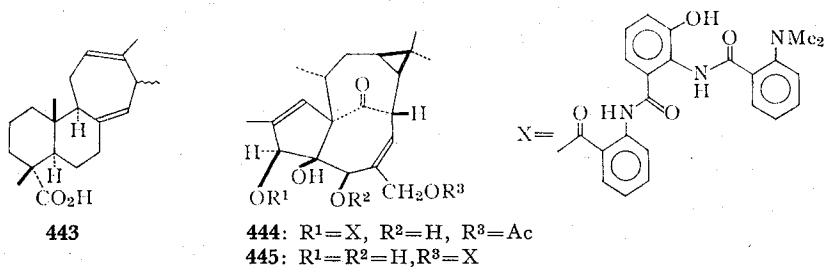


A short review for phorbol esters and their physiological activity was published in Japanese.<sup>226)</sup> Stimulation for choline incorporation was recognized in phorbol esters.<sup>227)</sup>

Irradiation of several 4 $\alpha$ -phorbol derivatives (**439**) with UV light of 254 nm yielded the isomeric lumi-products (**440**).<sup>228)</sup>

Structure **441** of 7-hydroxylathyrol, a further diterpene from *Euphorbia lathyris*, was confirmed and extended by X-ray diffraction analysis of **442**.<sup>229)</sup>

The structure of strobic acid, a new resin acid from *Pinus strobus*, was shown to be **443**.<sup>230)</sup>



Isolation of two new alkaloids, milliamines A and B, from the roots of *Euphorbia Millii* and their structure elucidation were reported. Milliamines A and B were assigned structures **444** and **445**, respectively.<sup>231)</sup>

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